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FORM PTO-1390

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER PF-0662 USN

US APPLICATION NO TO BE ASSIGNED

INTERNATIONAL APPLICATION NO PCT/US00/02237

INTERNATIONAL FILING DATE 28 January 2000

PRIORITY DATE CLAIMED 29 January 1999

TITLE OF INVENTION

CANCER-ASSOCIATED PROTEINS

APPLICANT(S) FOR DO/EO/US

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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

- 1. 

   This is the FIRST submission of items concerning a filing under 35 U.S.C. 371.
- 2. 

  This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
- 3. 

  This is an express request to promptly begin national examination procedures (35 U.S.C. 371 (f)).
- 4. □ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
- - a.  $\square$  is attached hereto (required only if not communicated by the International Bureau)
  - b.  $\square$  has been communicated by the International Bureau.
  - c. \( \text{is not required, as the application was filed in the United States Receiving Office (RO/US).
- 6. □ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
- - a.  $\square$  are attached hereto (required only if not communicated by the International Bureau).
  - b.  $\square$  have been communicated by the International Bureau.
  - c. 

    have not been made; however, the time limit for making such amendments has NOT expired.
- 8. □ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(e)(3)).
- 9. □ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
- 10.□ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

# Items 11 to 16 below concern document(s) or information included:

- 11. □ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
- 12. □ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.27 and 3 31 is included.
- 13. □ A FIRST preliminary amendment.
  - ☐ A SECOND or SUBSEQUENT preliminary amendment.
- 14. □ A substitute specification.
- 15. □ A change of power of attorney and/or address letter.
- 1) Transmittal Letter (2 pp, in duplicate)
- 2) Return Postcard
- 3) Express Mail Label No.: EL 856 154 129 US
- 4) Request to Transfer

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ENTER APPROPRIATE BASIC FEE AMOUNT =					\$690.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than $\Box$ 20 $\Box$ 30 months from the earliest claimed priority date (37 CFR 1 492(e)).					\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE			
Total Claims	23 =	3	X \$ 18.00		\$ 54.00	
Independent Chims	2 =	0	X \$ 80.00		\$	
MULTIPLE DEPENDENT CLAIM(S) (1f applicable) + \$270.00					\$	
TOTAL OF ABOVE CALCULATIONS =					\$744.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.					\$	
SUBTOTAL =					\$744.00	
Processing fee of \$130.00 for furnishing the Engish translation later than \$\Bigsq\$ 20 \$\Bigsq\$ 30 months from the earliest clailmed priority date (37 CFR 1492(f)). +					\$	
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Fee for recording the encosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by the appropriate cover sheet (37 CFR 3.28, 3 31) \$40.00 per property +					\$	
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I		NAME: Diana Haml	et-Cox			

REGISTRATION NUMBER: 33,302

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#### **NUCLEIC-ACID BINDING PROTEINS**

#### TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of nucleic-acid binding proteins and to the use of these sequences in the diagnosis, treatment, and prevention of reproductive, immune, and neurological disorders, and cell proliferative disorders including cancer.

### BACKGROUND OF THE INVENTION

Multicellular organisms are comprised of diverse cell types that differ dramatically both in structure and function. The identity of a cell is determined by its characteristic pattern of gene expression, and different cell types express overlapping but distinct sets of genes throughout development. Spatial and temporal regulation of gene expression is critical for the control of cell proliferation, cell differentiation, apoptosis, and other processes that contribute to organismal development. Furthermore, gene expression is regulated in response to extracellular signals that mediate cell-cell communication and coordinate the activities of different cell types. Appropriate gene regulation also ensures that cells function efficiently by expressing only those genes whose functions are required at a given time.

Transcriptional regulatory proteins are essential for the control of gene expression. Some of these proteins function as transcription factors that initiate, activate, repress, or terminate gene transcription. Transcription factors generally bind to promoter, enhancer, or upstream regulatory regions of a gene in a sequence-specific manner, although some factors bind regulatory elements within or downstream of the coding region. Transcription factors may bind to a specific region of DNA singly or as a complex with other accessory factors. (Reviewed in Lewin, B. (1990) Genes IV, Oxford University Press, New York, NY, pp. 554-570.)

The double helix structure and repeated sequences of DNA create topological and chemical features which can be recognized by transcription factors. These features include hydrogen bond donor and acceptor groups, hydrophobic patches, major and minor grooves, and regular repeated stretches of sequence which induce distinct bends in the helix. Typically, transcription factors recognize specific DNA sequence motifs of about 20 nucleotides in length. Multiple adjacent transcription factor-binding motifs may be required for gene regulation.

Many transcription factors incorporate DNA-binding structural motifs which comprise either α helices or β sheets that bind to the major groove of DNA. Four well-characterized structural motifs are helix-turn-helix, zinc finger, leucine zipper, and helix-loop-helix. Proteins containing these motifs may act alone as monomers or form homo- or heterodimers that interact with DNA.

The helix-turn-helix motif consists of two a helices connected at a fixed angle by a short

chain of amino acids. One of the helices binds to the major groove. Helix-turn-helix motifs are exemplified by the homeobox motif which is present in homeodomain proteins. These proteins are critical for specifying the anterior-posterior body axis during development and are conserved throughout the animal kingdom. The Antennapedia and Ultrabithorax proteins of <u>Drosophila</u> melanogaster are prototypical homeodomain proteins. (Pabo, C.O. and R.T. Sauer (1992) Ann. Rev. Biochem. 61:1053-1095.)

The zinc finger motif, which binds zinc ions, generally contains tandem repeats of about 30 amino acids consisting of periodically spaced cysteine and histidine residues. Examples of this sequence pattern include the C2H2-type and the C3HC4-type zinc fingers, and the PHD domain. (Lewin, supra; Aasland, R., et al. (1995) Trends Biochem. Sci 20:56 - 59.) Zinc finger proteins each contain an  $\alpha$  helix and an antiparallel  $\beta$  sheet whose proximity and conformation are maintained by the zinc ion. Contact with DNA is made by the arginine preceding the  $\alpha$  helix and by the second, third, and sixth residues of the  $\alpha$  helix. Variants of the zinc finger motif include poorly defined cysteine-rich motifs which bind zinc or other metal ions. These motifs may not contain histidine residues and are generally nonrepetitive.

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The leucine zipper motif comprises a stretch of amino acids rich in leucine which can form an amphipathic  $\alpha$  helix. This structure provides the basis for dimerization of two leucine zipper proteins. The region adjacent to the leucine zipper is usually basic, and upon protein dimerization, is optimally positioned for binding to the major groove. Proteins containing such motifs are generally referred to as bZIP transcription factors.

The helix-loop-helix motif (HLH) consists of a short  $\alpha$  helix connected by a loop to a longer  $\alpha$  helix. The loop is flexible and allows the two helices to fold back against each other and to bind to DNA. The transcription factor Myc contains a prototypical HLH motif.

Most transcription factors contain characteristic DNA binding motifs, and variations on the above motifs and new motifs have been and are currently being characterized. (Faisst, S. and S. Meyer (1992) Nucl. Acids Res. 20:3-26.)

Mutations in transcription factors contribute to oncogenesis. This is likely due to the role of transcription factors in the expression of genes involved in cell proliferation. For example, mutations in transcription factors encoded by proto-oncogenes, such as Fos, Jun, Myc, Rel, and Spil, may be oncogenic due to increased stimulation of cell proliferation. Conversely, mutations in transcription factors encoded by tumor suppressor genes, such as p53, RBl, and WTl, may be oncogenic due to decreased inhibition of cell proliferation. (Latchman, D. (1995) Gene Regulation: A Eukaryotic Perspective, Chapman and Hall, London, UK, pp 242-255.)

Gene expression is also affected by chromatin-associated proteins. In the nucleus, DNA is

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packaged into chromatin, the compact organization of which limits the accessibility of DNA to transcription factors and plays a key role in gene regulation. (Lewin, supra, pp. 409-410.) The compact structure of chromatin is determined and influenced by chromatin-associated proteins such as histones, high mobility group (HMG) proteins, helicases, and chromodomain proteins. There are five classes of histones, H1, H2A, H2B, H3, and H4, all of which are highly basic, low molecular weight proteins. The fundamental unit of chromatin, the nucleosome, consists of 200 base pairs of DNA associated with two copies each of H2A, H2B, H3, and H4. H1 links adjacent nucleosomes. HMG proteins are low molecular weight, non-histone proteins that may play a role in unwinding DNA and stabilizing single-stranded DNA. Helicases, which are DNA-dependent ATPases, unwind DNA, allowing access for transcription factors. Chromodomain proteins play a key role in the formation of highly-compacted, transcriptionally silent heterochromatin.

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Much of the regulation of gene expression in eucaryotic cells occurs at the posttranscriptional level. Messenger RNAs (mRNA), which are produced in the cell nucleus from primary transcripts of protein-encoding genes, are processed and transported to the cytoplasm where the protein synthesis machinery is located. RNA-binding proteins are a group of proteins that participate in the processing, editing, transport, localization, and posttranscriptional regulation of mRNAs, and comprise the protein component of ribosomes as well. The RNA-binding activity of many of these proteins is mediated by a series of RNA-binding motifs identified within them. These domains include the RNP motif, the arginine-rich motif, the RGG box, and the KH motif. (Reviewed in Burd, C. G. and Dreyfuss, G. (1994) Science 265:615 - 621.) The RNP motif is the most widely found and best characterized of these motifs. The RNP motif is composed of 90-100 amino acids which form an RNA-binding domain and is found in one or more copies in proteins that bind pre-mRNA, mRNA, pre-ribosomal RNA, and small nuclear RNAs. The RNP motif is composed of two short sequences (RNP-1 and RNP-2) and a number of other mostly hydrophobic, conserved amino acids interspersed throughout the motif. (Burd, supra; ExPASy PROSITE document PDOC0030.)

Many neoplastic disorders in humans can be attributed to inappropriate gene expression. Malignant cell growth may result from either excessive expression of tumor promoting genes or insufficient expression of tumor suppressor genes. (Cleary, M.L. (1992) Cancer Surv. 15:89-104.) Chromosomal translocations may also produce chimeric loci which fuse the coding sequence of one gene with the regulatory regions of a second unrelated gene. Such an arrangement often results in inappropriate gene transcription. The Wilms tumor suppressor gene product, WT1, is a protein containing a DNA-binding domain consisting of four zinc fingers and a proline-glutamine rich region capable of regulating transcription. (ExPASy PROSITE document PR00049.) Deletions of the WT1 gene, or point mutations which destroy the DNA-binding activity of the protein are associated with development of the pediatric nephroblastoma, Wilms tumor, and Denys-Drash syndrome. (Rauscher,

# F.J. (1993) FASEB J. 7:896-903.)

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Certain proteins enriched in glutamine are associated with various neurological disorders including spinocerebellar ataxia, bipolar effective disorder, schizophrenia, and autism. (Margolis, R.L. et al. (1997) Human Genetics 100:114-122.) These proteins contain regions with as many as 15 or more consecutive glutamine residues and may function as transcription factors with a potential role in regulation of neurodevelopment or neuroplasticity.

The immune system responds to infection or trauma by activating a cascade of events that coordinate the progressive selection, amplification, and mobilization of cellular defense mechanisms. A complex and balanced program of gene activation and repression is involved in this process. However, hyperactivity of the immune system as a result of improper or insufficient regulation of gene expression may result in considerable tissue or organ damage. This damage is well documented in immunological responses associated with arthritis, allergens, heart attack, stroke, and infections. (Harrison's Principles of Internal Medicine, 13/e, McGraw Hill, Inc. and Teton Data Systems Software, 1996.) In particular, a zinc finger protein termed Staf50 (for Stimulated trans-acting factor of 50 kDa) is a transcriptional regulator and is induced in various cell lines by interferon-I and -II. Staf50 appears to mediate the antiviral activity of interferon by down-regulating the viral transcription directed by the long terminal repeat promoter region of human immunodeficiency virus type-1 in transfected cells. (Tissot, C. (1995) J. Biol. Chem. 270:14891-14898.)

Furthermore, the generation of multicellular organisms is based upon the induction and coordination of cell differentiation at the appropriate stages of development. Central to this process is differential gene expression, which confers the distinct identities of cells and tissues throughout the body. Failure to regulate gene expression during development could result in developmental disorders.

The discovery of new nucleic-acid binding proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of reproductive, immune, and neurological disorders, and cell proliferative disorders including cancer.

## SUMMARY OF THE INVENTION

The invention features purified polypeptides, protnames, referred to collectively as "ABBR" and individually as "NuABP-1," "NuABP-2," "NuABP-3," "NuABP-4," "NuABP-5," "NuABP-6," "NuABP-7," "NuABP-8," "NuABP-9," "NuABP-10" "NuABP-11," "NuABP-12," "NuABP-13," "NuABP-14," "NuABP-15," "NuABP-16," "NuABP-17," "NuABP-18," "NuABP-19," "NuABP-20," "NuABP-21," "NuABP-22," "NuABP-23," "NuABP-24," "NuABP-25," "NuABP-26," "NuABP-27," "NuABP-28," "NuABP-29," "NuABP-30," "NuABP-31," "NuABP-32," "NuABP-33,"

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"NuABP-34," "NuABP-35," "NuABP-36," "NuABP-37," "NuABP-38," "NuABP-39." "NuABP-40" "NuABP-41," "NuABP-42," "NuABP-43," "NuABP-44," "NuABP-45," "NuABP-46." "NuABP-47," "NuABP-48," "NuABP-49," "NuABP-50" "NuABP-51," "NuABP-52," "NuABP-53," "NuABP-54," and "NuABP-55." In one aspect, the invention provides an isolated polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-55.

The invention further provides an isolated polynucleotide encoding a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55. In one alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:56-110.

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Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55.

The invention further provides an isolated polynucleotide comprising a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:56-110, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:56-110, c) a polynucleotide sequence complementary to a), or d) a polynucleotide sequence complementary to b). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

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Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:56-110, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence complementary to a), or d) a polynucleotide sequence complementary to b). The method comprises a) hybridizing the sample with a probe comprising at least 16 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide, and b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof. In one alternative, the probe comprises at least 30 contiguous nucleotides. In another alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a pharmaceutical composition comprising an effective amount of a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, and a pharmaceutically acceptable excipient. The invention additionally provides a method of treating a disease or condition associated with decreased expression of functional NuABP, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional NuABP, comprising administering to a patient in need of such treatment the pharmaceutical composition.

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Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional NuABP, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:56-110, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

#### BRIEF DESCRIPTION OF THE TABLES

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding NuABP.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of NuABP.

Table 3 shows selected fragments of each nucleic acid sequence: the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding NuABP were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze NuABP, along with applicable descriptions, references, and threshold parameters.

# **DESCRIPTION OF THE INVENTION**

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

# **DEFINITIONS**

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"NuABP" refers to the amino acid sequences of substantially purified NuABP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of

NuABP. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of NuABP either by directly interacting with NuABP or by acting on components of the biological pathway in which NuABP participates.

An "allelic variant" is an alternative form of the gene encoding NuABP. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

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"Altered" nucleic acid sequences encoding NuABP include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as NuABP or a polypeptide with at least one functional characteristic of NuABP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding NuABP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding NuABP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent NuABP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of NuABP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of NuABP. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of NuABP either by directly interacting with NuABP or by acting on components of the biological pathway in which NuABP participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')<sub>2</sub>, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind NuABP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

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The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell, the complementary nucleotides combine with natural sequences produced by the cell to form duplexes and to block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic NuABP, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The terms "complementary" and "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that total complementarity exists between the single stranded molecules. The degree of complementarity

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between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acid strands, and in the design and use of peptide nucleic acid (PNA) molecules.

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A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding NuABP or fragments of NuABP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using the XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of one or more Incyte Clones and, in some cases, one or more public domain ESTs, using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that, when made, least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

	Original Residue	Conservative Substitution
25	Ala	Gly, Ser
	Arg	His, Lys
	Asn	Asp, Gln, His
	Asp	Asn, Glu
	Cys	Ala, Ser
30	Gln	Asn, Glu, His
	Glu	Asp, Gln, His
	Gly	Ala
	His	Asn, Arg, Gln, Glu
	Ile	Leu, Val
35	Leu	Ile, Val
	Lys	Arg, Gln, Glu
	Met	Leu, Ile
	Phe	His, Met, Leu, Trp, Tyr
	Ser	Cys, Thr
40	Thr	Ser, Val

Trp	Phe, Tyr
Tyr	His, Phe, Trp
Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

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A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "fragment" is a unique portion of NuABP or the polynucleotide encoding NuABP which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:56-110 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:56-110, for example, as distinct from any other sequence in the same genome. A fragment of SEQ ID NO:56-110 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:56-110 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:56-110 and the region of SEQ ID NO:56-110 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-55 is encoded by a fragment of SEQ ID NO:56-110. A

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fragment of SEQ ID NO:1-55 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-55. For example, a fragment of SEQ ID NO:1-55 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-55. The precise length of a fragment of SEQ ID NO:1-55 and the region of SEQ ID NO:1-55 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

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The phrases "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequence pairs.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at

http://www.ncbi.nlm.nih.gov/BLAST/. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at http://www.ncbi.nlm.nih.gov/gorf/bl2.html. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

15 Reward for match: 1

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Penalty for mismatch: -2

Open Gap: 5 and Extension Gap: 2 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 11

Filter: on

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some

alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the hydrophobicity and acidity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) with blastp set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Open Gap: 11 and Extension Gap: 1 penalties

Gap x drop-off: 50

Expect: 10

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Word Size: 3

Filter: on

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of identity. Specific

hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Generally, such wash temperatures are selected to be about  $5^{\circ}$ C to  $20^{\circ}$ C lower than the thermal melting point  $(T_m)$  for the specific sequence at a defined ionic strength and pH. The  $T_m$  is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating  $T_m$  and conditions for nucleic acid hybridization are well known and can be found in Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual,  $2^{nd}$  ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

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High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g.,  $C_0$ t or  $R_0$ t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide

sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" and "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

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The term "modulate" refers to a change in the activity of NuABP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of NuABP.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Generally, operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Probe" refers to nucleic acid sequences encoding NuABP, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes.

"Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also

be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel et al., 1987, Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis et al., 1990, PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

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Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence.

This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook. <a href="superaction-nucleic acids">supra</a>. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be use to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

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The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding NuABP, or fragments thereof, or NuABP itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by different amino acids or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

"Transformation" describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected

based on the type of host cell being transformed and may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

### 30 THE INVENTION

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The invention is based on the discovery of new human nucleic-acid binding proteins (NuABP), the polynucleotides encoding NuABP, and the use of these compositions for the diagnosis, treatment, or prevention of reproductive, immune, and neurological disorders, and cell proliferative disorders including cancer.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding

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NuABP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each NuABP were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. The Incyte clones in column 5 were used to assemble the consensus nucleotide sequence of each NuABP and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows identification or homologous sequences as identified by BLAST analysis; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods of column 7 were used to characterize each polypeptide through sequence homology and protein motifs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding NuABP. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1. These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:56-110 and to distinguish between SEQ ID NO:56-110 and related polynucleotide sequences. The polypeptides encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue categories which express NuABP as a fraction of total tissues expressing NuABP. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing NuABP as a fraction of total tissues expressing NuABP. Of particular note is the expression of SEQ ID NO:83 and SEQ ID NO:110 in neurological tissue. About 53% of the cDNA libraries expressing SEQ ID NO:83 are derived from neurological tissue. Furthermore, SEQ ID NO:110 expression is detected exclusively in a cDNA library derived from brain tissue afflicted with Huntington's disease. Column 5 lists the vectors used to subclone each cDNA library.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding NuABP were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

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Fragments of the nucleotide sequences encoding NuABP are useful, for example, in hybridization or amplification technologies to identify SEQ ID NOS:56-110 and to distinguish between SEQ ID NOS:56-110 and related polynucleotide sequences. The polypeptides encoded by

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these fragments are useful, for example, as immunogenic peptides.

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The invention also encompasses NuABP variants. A preferred NuABP variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the NuABP amino acid sequence, and which contains at least one functional or structural characteristic of NuABP.

The invention also encompasses polynucleotides which encode NuABP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:56-110, which encodes NuABP.

The invention also encompasses a variant of a polynucleotide sequence encoding NuABP. In particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding NuABP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:56-110 which has at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:56-110. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of NuABP.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding NuABP, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring NuABP, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode NuABP and its variants are generally capable of hybridizing to the nucleotide sequence of the naturally occurring NuABP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding NuABP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding NuABP and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode NuABP and NuABP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding NuABP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:56-110 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

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Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Perkin-Elmer). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Perkin-Elmer), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding NuABP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al.

(1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-3060). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

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When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode NuABP may be cloned in recombinant DNA molecules that direct expression of NuABP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express NuABP.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter NuABP-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-

mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In another embodiment, sequences encoding NuABP may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.)

Alternatively, NuABP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of NuABP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) <u>Proteins, Structures and Molecular Properties</u>, WH Freeman, New York NY.)

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In order to express a biologically active NuABP, the nucleotide sequences encoding NuABP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers. constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding NuABP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding NuABP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding NuABP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an inframe ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding NuABP and appropriate transcriptional and translational control elements. These methods include <u>in vitro</u> recombinant DNA techniques, synthetic techniques,

and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

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A variety of expression vector/host systems may be utilized to contain and express sequences encoding NuABP. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding NuABP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding NuABP can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1 plasmid (Life Technologies). Ligation of sequences encoding NuABP into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of NuABP are needed, e.g. for the production of antibodies, vectors which direct high level expression of NuABP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of NuABP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast <u>Saccharomyces cerevisiae</u> or <u>Pichia pastoris</u>. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, <u>supra</u>; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; and Scorer, C.A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of NuABP. Transcription of sequences encoding NuABP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al.

(1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.)

These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., <u>The McGraw Hill Yearbook of Science and Technology</u> (1992) McGraw Hill, New York NY, pp. 191-196.)

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In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding NuABP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses NuABP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of NuABP in cell lines is preferred. For example, sequences encoding NuABP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk* and *apr* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which

alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), β glucuronidase and its substrate β-glucuronide. or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding NuABP is inserted within a marker gene sequence, transformed cells containing sequences encoding NuABP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding NuABP under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

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In general, host cells that contain the nucleic acid sequence encoding NuABP and that express NuABP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of NuABP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on NuABP is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding NuABP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding NuABP, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase

such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding NuABP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode NuABP may be designed to contain signal sequences which direct secretion of NuABP through a prokaryotic or eukaryotic cell membrane.

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In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention. natural, modified, or recombinant nucleic acid sequences encoding NuABP may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric NuABP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of NuABP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the NuABP encoding sequence and the heterologous protein sequence, so that NuABP may be cleaved away from the heterologous moiety following purification.

Methods for fusion protein expression and purification are discussed in Ausubel (1995, <u>supra</u>, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled NuABP may be achieved <u>in vitro</u> using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, <sup>35</sup>S-methionine.

Fragments of NuABP may be produced not only by recombinant means, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A peptide synthesizer (Perkin-Elmer). Various fragments of NuABP may be synthesized separately and then combined to produce the full length molecule.

#### **THERAPEUTICS**

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Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of NuABP and nucleic-acid binding proteins. In addition, the expression of NuABP is closely associated with proliferative, neuronal, inflamed, and cancerous tissues and tissues of the reproductive system. Therefore, NuABP appears to play a role in reproductive, immune, and neurological disorders, and cell proliferative disorders including cancer. In the treatment of disorders associated with increased NuABP expression or activity, it is desirable to decrease the expression or activity of NuABP. In the treatment of disorders associated with decreased NuABP expression or activity, it is desirable to increase the expression or activity of NuABP.

Therefore, in one embodiment, NuABP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of NuABP. Examples of such disorders include, but are not limited to, a reproductive disorder such as disorders of prolactin production, infertility, including tubal disease, ovulatory defects, and endometriosis, disruptions of the estrous cycle, disruptions of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, endometrial and ovarian tumors, uterine fibroids, autoimmune disorders, ectopic pregnancies, and teratogenesis; cancer of the breast, fibrocystic breast disease, and galactorrhea; disruptions of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia; an immune disorder such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis,

cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis. Goodpasture's syndrome, gout, Graves' disease. Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis. scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, trauma, and hematopoietic cancer including lymphoma, leukemia, and myeloma; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease. Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; and a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus.

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In another embodiment, a vector capable of expressing NuABP or a fragment or derivative

thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of NuABP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified NuABP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of NuABP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of NuABP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of NuABP including, but not limited to, those listed above.

In a further embodiment, an antagonist of NuABP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of NuABP. Examples of such disorders include, but are not limited to, those reproductive, immune, and neurological disorders, and cell proliferative disorders including cancer, described above. In one aspect, an antibody which specifically binds NuABP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express NuABP.

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In an additional embodiment, a vector expressing the complement of the polynucleotide encoding NuABP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of NuABP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of NuABP may be produced using methods which are generally known in the art. In particular, purified NuABP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind NuABP. Antibodies to NuABP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with NuABP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to

increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans. BCG (bacilli Calmette-Guerin) and <u>Corynebacterium parvum</u> are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to NuABP have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of NuABP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

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Monoclonal antibodies to NuABP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce NuABP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for NuABP may also be generated. For example, such fragments include, but are not limited to,  $F(ab')_2$  fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the  $F(ab')_2$  fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D.

et al. (1989) Science 246:1275-1281.)

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Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between NuABP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering NuABP epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for NuABP. Affinity is expressed as an association constant, K<sub>a</sub>, which is defined as the molar concentration of NuABP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K<sub>a</sub> determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple NuABP epitopes, represents the average affinity, or avidity, of the antibodies for NuABP. The K<sub>a</sub> determined for a preparation of monoclonal antibodies, which are monospecific for a particular NuABP epitope, represents a true measure of affinity. High-affinity antibody preparations with K<sub>a</sub> ranging from about 10° to 10¹² L/mole are preferred for use in immunoassays in which the NuABP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K<sub>a</sub> ranging from about 10° to 10² L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of NuABP, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J.E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of NuABP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding NuABP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding NuABP may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with sequences complementary to polynucleotides encoding NuABP. Thus, complementary molecules or

fragments may be used to modulate NuABP activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding NuABP.

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Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding NuABP. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

Genes encoding NuABP can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding NuABP. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding NuABP. Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may be employed. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding NuABP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides,

corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

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Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding NuABP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of NuABP, antibodies to NuABP, and mimetics, agonists, antagonists, or inhibitors of NuABP. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered

to a patient alone, or in combination with other agents. drugs, or hormones.

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The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to. oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, tale, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in

aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

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The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acids. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of NuABP, such labeling would include amount, frequency, and method of administration.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example NuABP or fragments thereof, antibodies of NuABP, and agonists, antagonists or inhibitors of NuABP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such

as by calculating the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population) or LD<sub>50</sub> (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD<sub>50</sub>/ED<sub>50</sub> ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED<sub>50</sub> with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1  $\mu$ g to 100,000  $\mu$ g, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

### **DIAGNOSTICS**

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In another embodiment, antibodies which specifically bind NuABP may be used for the diagnosis of disorders characterized by expression of NuABP, or in assays to monitor patients being treated with NuABP or agonists, antagonists, or inhibitors of NuABP. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for NuABP include methods which utilize the antibody and a label to detect NuABP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring NuABP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of NuABP expression. Normal or standard values for NuABP expression are established by combining body fluids or cell

extracts taken from normal mammalian subjects, for example, human subjects, with antibody to NuABP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of NuABP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding NuABP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of NuABP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of NuABP, and to monitor regulation of NuABP levels during therapeutic intervention.

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In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding NuABP or closely related molecules may be used to identify nucleic acid sequences which encode NuABP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding NuABP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the NuABP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:56-110 or from genomic sequences including promoters, enhancers, and introns of the NuABP gene.

Means for producing specific hybridization probes for DNAs encoding NuABP include the cloning of polynucleotide sequences encoding NuABP or NuABP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as <sup>32</sup>P or <sup>35</sup>S, or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding NuABP may be used for the diagnosis of disorders associated with expression of NuABP. Examples of such disorders include, but are not limited to, a reproductive disorder such as disorders of prolactin production, infertility, including tubal disease, ovulatory defects, and endometriosis, disruptions of the estrous cycle, disruptions of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, endometrial and ovarian tumors, uterine fibroids, autoimmune disorders, ectopic pregnancies, and teratogenesis; cancer of the

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breast, fibrocystic breast disease, and galactorrhea: disruptions of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia: an immune disorder such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis. osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, 15 ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, trauma, and hematopoietic cancer including lymphoma, leukemia, and myeloma; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke. cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, 20 progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the 25 nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, 30 endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; and a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal 35

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hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus. The polynucleotide sequences encoding NuABP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered NuABP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding NuABP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding NuABP may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding NuABP in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

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In order to provide a basis for the diagnosis of a disorder associated with expression of NuABP, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding NuABP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the

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development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

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Additional diagnostic uses for oligonucleotides designed from the sequences encoding NuABP may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding NuABP, or a fragment of a polynucleotide complementary to the polynucleotide encoding NuABP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

Methods which may also be used to quantify the expression of NuABP include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding NuABP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price,

C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

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Fluorescent <u>in situ</u> hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See. e.g., Heinz-Ulrich, et al. (1995) in Meyers, <u>supra</u>, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding NuABP on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, NuABP, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between NuABP and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with NuABP, or fragments thereof, and washed. Bound NuABP is then detected by methods well known in the art. Purified NuABP can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing

antibodies capable of binding NuABP specifically compete with a test compound for binding NuABP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with NuABP.

In additional embodiments, the nucleotide sequences which encode NuABP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. 60/117,905 and U.S. Ser. No. 60/117,904, are hereby expressly incorporated by reference.

20 EXAMPLES

### I. Construction of cDNA Libraries

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RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP

vector system (Stratagene) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, <u>supra</u>, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent <u>E. coli</u> cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5α, DH10B, or ElectroMAX DH10B from Life Technologies.

### II. Isolation of cDNA Clones

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Plasmids were recovered from host cells by <u>in vivo</u> excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

### III. Sequencing and Analysis

cDNA sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Perkin-Elmer) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the

ABI PRISM 373 or 377 sequencing system (Perkin-Elmer) in conjunction with standard ABI protocols and base calling software: or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

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The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID

NO:56-110. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

### IV. Northern Analysis

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Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, <u>supra</u>, ch. 7; Ausubel, 1995, <u>supra</u>, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

### % sequence identity x % maximum BLAST score

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15 The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding NuABP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

### V. Extension of NuABP Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:56-110 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target

sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

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High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg<sup>2-</sup>. (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, and β-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min: Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100  $\mu$ l PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5  $\mu$ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5  $\mu$ l to 10  $\mu$ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent <u>E. coli</u> cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min;

Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethysulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequences of SEQ ID NO:56-110 are used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

### VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:56-110 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250  $\mu$ Ci of [ $\gamma$ - $^{32}$ P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing  $10^7$  counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and compared.

### VII. Microarrays

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A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, <u>supra</u>.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe

which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

Full-length cDNAs, Expressed Sequence Tags (ESTs). or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

### VIII. Complementary Polynucleotides

Sequences complementary to the NuABP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring NuABP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of NuABP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the NuABP-encoding transcript.

### IX. Expression of NuABP

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Expression and purification of NuABP is achieved using bacterial or virus-based expression systems. For expression of NuABP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express NuABP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of NuABP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant <u>Autographica californica</u> nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding NuABP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to

infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, NuABP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from NuABP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified NuABP obtained by these methods can be used directly in the following activity assay.

### X. Demonstration of NuABP Activity

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NuABP activity is measured by its ability to stimulate transcription of a reporter gene (Liu, H.Y. et al. (1997) EMBO J. 16(17):5289-5298.) The assay entails the use of a well characterized reporter gene construct, LexA<sub>op</sub>-LacZ, that consists of LexA DNA transcriptional control elements (LexA<sub>op</sub>) fused to sequences encoding the <u>E. coli</u> LacZ enzyme. The methods for constructing and expressing fusions genes, introducing them into cells, and measuring LacZ enzyme activity, are well known to those skilled in the art. Sequences encoding NuABP are cloned into a plasmid that directs the synthesis of a fusion protein, LexA-NuABP, consisting of NuABP and a DNA binding domain derived from the LexA transcription factor. The resulting plasmid, encoding a LexA-NuABP fusion protein, is introduced into yeast cells along with a plasmid containing the LexA<sub>op</sub>-LacZ reporter gene. The amount of LacZ enzyme activity associated with LexA-NuABP transfected cells, relative to control cells, is proportional to the amount of transcription stimulated by the NuABP.

### XI. Functional Assays

NuABP function is assessed by expressing the sequences encoding NuABP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10  $\mu$ g of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell

高山地区 医精神病 基础 经运货营销 化二氯 医上皮压 医医囊肿管 医阴囊 解毒性

line, using either liposome formulations or electroporation. 1-2  $\mu$ g of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of NuABP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding NuABP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding NuABP and other genes of interest can be analyzed by northern analysis or microarray techniques.

### XII. Production of NuABP Specific Antibodies

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NuABP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the NuABP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase

immunogenicity. (See, e.g., Ausubel, 1995, <u>supra.</u>) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-NuABP activity by, for example, binding the peptide or NuABP to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

### XIII. Purification of Naturally Occurring NuABP Using Specific Antibodies

Naturally occurring or recombinant NuABP is substantially purified by immunoaffinity chromatography using antibodies specific for NuABP. An immunoaffinity column is constructed by covalently coupling anti-NuABP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing NuABP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of NuABP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/NuABP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and NuABP is collected.

### XIV. Identification of Molecules Which Interact with NuABP

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NuABP, or biologically active fragments thereof, are labeled with <sup>125</sup>I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) Biochem. J. 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled NuABP, washed, and any wells with labeled NuABP complex are assayed. Data obtained using different concentrations of NuABP are used to calculate values for the number, affinity, and association of NuABP with the candidate molecules.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

### TABLE

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
. 1	56	025733	SPLNFET01	025733H1 and 025733X307D2 (SPLNFET01), 1519809F1 and 1519809T1 (BLADTUT04), 1526288T6 (UCMCL5T01), 1595557X16C1 and 1595557X19C1 (BRAINOT14), 1903359F6 (OVARNOT07), 2417225F6 (HNT3AZT01), 4283542H1 (LIVRDIR01)
7	57	079702	SYNORAB01	002190H1 (U937NOT01), 079479F1 and 079702H1 (SYNORAB01), 125223T6 (LUNGNOT01), 371006R6 (LUNGNOT02), 2129460T6 (KIDNNOT05), 2999366H1 (TLYMNOT06), 3031905F6 (TLYMNOT05), 4949863H1 (SINTNOT25)
3	58	116208	KIDNNOT01	116208H1 and 116208R1 (KIDNNOTO1), 2293058R6 (BRAINONO1), 3731418H1 and 3731418T6 (SMCCNONO3)
4	59	179261	PLACNOB01	179261H1 (PLACNOB01), 3666231F6 and 3666231T6 (PANCNOT16)
ιΩ	09	259161	HNT2RAT01	- [-
φ 55	61	320087	EOSIHET02	016657F1 (HUVELPB01), 320087H1 (EOSIHET02), 824110R1 (PROSNOT06), 987467H1 (LVENNOT03), 1235752F1 (LUNGFET03), 1361280F1 (LUNGNOT12), 1389740H1 (EOSINOT01), 1534332F1 (SPLNNOT04), 1813754F6 (SKINBIT01), 4184915H1 (BRSTNOT31), 5306522H1 (MONOTXT02)
7	62	491271	HNT2AGT01	363816X3 and 363816X9 (PROSNOTO1), 491271F1, 491271H1 and 491271T6 (HNT2AGT01), 967354R6, 967354X15 and 967354X27 (BRSTNOT05), 273344H1 (OVARTUT04)
ω	63	585172	PROSNOT02	395188R6 (TMLR2DT01), 585172H1 (PROSNOT02), 864269T1 (BRAITUT03), 1417965F1 (KIDNNOT09)
6	64	615200	COLNTUT02	615200H1 and 615200R6 (COLNTUTO2), 1213980R1 (BRSTTUT01), SBPA02731D1, SBPA00184D1
10	65	997067	KIDNTUT01	125981X3 (LUNGNOTO1), 997067H1, 997067R6 and 997067T6 (KIDNTUTO1), 1448201H1 (PLACNOTO2), 1663447H1 (BRSTNOTO9), 1889314H1 (BLADTUTO7), 1918706H1 (PROSNOTO6), 2699956H1 (OVARTUT10), 2702585H1 (OVARTUT10), 2900479H1 (DRGCNOTO1), 3595727T6 (FIBPNOTO1), 4309131H1 (BRAUNOTO1)
11	99	144326 2	THYRNOT03	1257005F1 (MENITUTO3), 1443262H1 (THYRNOTO3), 1618906F6 (BRAITUT12), 2474133T6 (THP1NOTO3), 3594075H1 (FIBPNOTO1), 4914442H1 (LIVRFETO5)

Processin Nucleotide						
122164   BLADTUTO4   152164H and 1522364FI (RERANOTO2), 136178HI   1868549   173082   168549   173080X14 and 903980X14 and 903980X17 (COLINIOTO7)   173082   1868649   173082X121C (BRSTNOTO3), 137   186464   173082X12CI and 1730829X13CI (BRSTYUTO8), 186464   173082X12CI and 1730829X13CI (BRSTYUTO8), 186464   173082   1730829X12CI and 1730829X13CI (BRSTYUTO8), 1864641HI   1	Pr. SE	otein 12 ID NO:	Nucleotide SEQ ID NO:	Clone	Library	Fragments
13   68   168549   PROSNOTI5   416412776 (BRSTNOT32)     14   69		12	29	152164 8	BLADTUT04	292172H1 (TMLR3DT01), 819925R6 (KERANOT02), 1353913H1 (LATRTUT02), 1521648H1 and 1522364F1 (BLADTUT04), 1963178H1 (BRSTNOT04), 2342505F6 (TESTTUT02), 4899970H1 (OVARDIT01), 5043585H2 (PLACFER01)
14   69   173082   BRSTTUTO8   116146R1 (KIDNNOTO1),   186464   PROSNOT19   1884972H1 (PROSNOT26),   1844972H1 (COLNNOTO8),   184466   THPINOTO3   1506658F1 (BRAITUTO7),   187   24450   THPINOTO3   1506658F1 (BRAITUTO1),   190131276 (BLADTUTO1),   190131276 (BLADTUTO6),   396323R6 (PITUNOTO2),   257246   HIPOAZTO1   (HIPOAZTO1), 2650980F6 (COLCTUTO3)   2345947H1 (CARGDITO1), 2650980F6 (COLCTUTO3)   2345405   BRSTNOT13   261399H1 (HNT2AGTO1), 2650980F6 (COLCTUTO3)   2345405   ADRENOT09   2496984F6 (ADRETUTO2),   2446051H1 (KIDNITUT15), 3454051H1 (KIDNITUT15), 3454051H1   (KIDNITUT15), 3454051H1		13	68	168549 4	PROSNOT15	903980X14 and 903980X17 (COLNNOT07) (BRSTNOT32)
15   70   186464   PROSNOT19   1844972H1 (COLNNOT08)   1		14	69	173082 9	BRSTTUT08	116146R1 (KIDNNOT01), 836856R1 (PROSNOT07), 1730829H1, 1730829X11C1, 1730829X12C1 and 1730829X13C1 (BRSTTUT08), 1959889R6 (BRSTNOT04), 2188079H1 (PROSNOT26), 3384625H1 (ESOGNOT04)
16 71 244460 THPINOTO3 1506658F1 (BRAITUTO7)  17  244500 THPINOTO3 819194R1 (KERANOTO2),  18  73 257246 HIPOAZTO1 (LUNGFETO3), 2345947H  20 74 257289 HIPOAZTO1 (LUNGFETO3), 2650980F(COLCTUTO3)  20 75 278567 BRSTNOT13 261399H1 (HNT2AGTO1), 9  21 76 279747 NPOLNOTO1 251389H1 (ANT2AGTO1), 9  22 77 296064 ADRENOTO9 2496984F6 (ADRETUTOS), 2496984F6 (LIVRNOTOS), 2496984F6 (LIVRNOTOS), 2496984F6 (LIVRNOTOS), 2496981H1 (KIDNTUTIS), 3454051H1 (KIDNTUTIS), 3454051H11 (KIDNTUTIS), 3454051H11		15	70	186464 1		1844972H1 (COLNNOTO8), 1864641F6 and 1864641H1 (PROSNOT19), 3090702T6 (BRSTNOT19), 3411665H1 (BRSTUS08), 5152366H1 (HEARFET03), 5166179H1 (MUSCDMT01)
17 72 244500 THPINOTO3 819194R1 (KERANOTO2), 819194R1 (KERANOTO2), 1901312T6 (BLADTUT06) 396323R6 (PITUNOTO2), 257246 HIPOAZT01 (LUNGFETO3), 2345947H (COLCTUTO3) (COLCTUTO3) 257289 HIPOAZT01 1275514T6 (TESTTUT02), 279747 NPOLNOTO1 302614X13 (TESTNOTO4), 9 257289 ADRENOTO9 2496984F6 (ADRETUTO5), 296064 ADRENOTO1 279331R6 (LIVRNOTO2), 3454051H1 (KIDNTUT15), 3454051H1 (KIDNTUT15), 3454051H1 (KIDNTUT15), 3454051H1 (KIDNTUT15), 3454051H1		16	71	244460 4	THP1NOT03	(BRAITUT07),
73 257246 HIPOAZTO1 (LUNGFETO3), 2345947H;  74 257289 HIPOAZTO1 (COLCTUTO3)  75 4 HIPOAZTO1 (COLCTUTO3)  75 279747 NPOLNOTO1 (SAISOSHI (HNT2AGTO1), 2650980F, 279747  76 279747 NPOLNOTO1 SAIAOO739F1, SAIAOC537-99  77 296064 ADRENOTO9 (27211R1, 027211X1 and 02721X1X1 and 0272X1X1X1 and 0272XIXIX and 0272XIXIX and 0272XIXIX and 0272XIXIX and 0272XIXIX and 0272XIXIXI and 0272XIXIX and 0272XIXIXI and 0272XIXIXIXI and 0272XIXIXI and 0272XIXIXIXIXIXIXIXIXIXIXIXIXIXIXIXIXIXIX		17	72	244500 8	THP1NOT03	, 628644H1 1259467H1 , 2445008H1
74 257289 HIPOAZTO1 1275514T6 (TESTTUTO2), 278567 BRSTNOT13 261399H1 (HNT2AGTO1), 9 279747 NPOLNOT01 SAIA00739F1, SAIA025377 OF 296064 ADRENOT09 2496984F6 (ADRETUTO5), 1 1 279331R6 (LIVRNOT02), 1 1 (KIDNTUT15), 3454051H1		18	73	257246 2	HIPOAZT01	, 863622H1 (BRAITUTO3), 1848956F6 an H1 (TESTTUTO2), 2396384F6 (THP1AZTO1 F6 (LUNGTUT12), 2814325H1 (OVARNOT10
75 278567 BRSTNOT13 261399H1 (HNT2AGT01), 76 279747 NPOLNOT01 302614X13 (TESTNOT04), 9 SAIA00739F1, SAIA02537 77 296064 ADRENOT09 027211R1, 027211X1 and 0 027211R1, 027211X1 and 1 345405 SPLNNOT11 (KIDNTUT15), 3454051H1		19	74	257289 2	HIPOAZT01	نہا
76 279747 NPOLNOT01 302614X13 (TESTNOT04), 9 SAIA00739F1, SAIA0253: 0 296064 ADRENOT09 2496984F6 (ADRETUT05), 1 345405 SPLNNOT11 (KIDNTUT15), 3454051H1	. ,	20		278567 4	BRSTNOT13	61399H1 (HNT2AGT01), 1274739F1
77 296064 ADRENOT09 027211R1, 027211X1 and 0		21	76	279747 9	NPOLNOT01	ł
78 345405 SPLNNOT11 279331R6 (LIVRNOT02),	.,	22	77	296064 0	ADRENOT09	027211X1 and 027211X3 (ADRETUT05), 2960640H1
		23	78	345405 1	SPLNNOT11	2515972T6 and 2516010T6 (LIVRTUT04 1 (SPLNNOT11)

 FABLE 1 (cont.)

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	Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone	Library	Fragments
1	24	79	351064 0	CONCNOT01	556354H1 (MPHGLPT02), 581085H1 (BRAVTXT05), 990636R6 (COLNNOT11), 1799185F6 and 1799185F6 (COLNNOT27), 3510640H1 (CONCNOT01), 4326648H1 (TLYMUNT01), SBHA01099F1
<del> L</del>	25	80	381508 3	TONSNOT03	2026951R6 and 2026951T6 (KERANOT02), 2300211R6 (BRSTNOT05), 2505283F6 (CONUTUT01), 3187267R6 (THYMNON04), 3815083H1 and 3815083T6 (TONSNOT03)
<u>.</u>	26	81	398845 7	FUNGNONO3	609622R6 (COLNNOT01), 1710465F6 (PROSNOT16), 3988457H1 (LUNGNON03), SAQA00089F1, SAQA03055F1, SAQB00279F1
	27	82	131890	BMARNOT02	131890H1 (BMARNOT02), 131890T6 (BMARNOT02), 132849R6 (BMARNOT02), 3357071F6 (PROSTUT16)
i_	28	83	238642	SINTNOT02	238642H1 (SINTNOTO2), 1620593F6 (BRAITUT13), 1620593H1 (BRAITUT13), 1620593T6 (BRAITUT13), 2534087F6 (BRAINOT18)
	29	84	669862	CRBLNOT01	347231X7 (THYMNOT02), 669862H1 (CRBLNOT01), 2244458R6 (HIPONON02), 2244458T6 (HIPONON02), 2622610T6 (KERANOT02), 3536262H1 (KIDNNOT25), 4204212H1 (BRAITUT29)
<del>,  </del>	30	85	100366 3	BRSTNOT03	, 1003663H1 (BRSTNOT03), 1252179F2 (
	31	86	143255	BEPINON01	(BLADTUTO2), 1432557H1 (BEPINONO1), (DUODNOTO2), 2182184F6 (SINIMOTO1)
	32	87	144177 0	THYRNOT03	(HUVENOBO1), 1441770H1 (TUTRSNOT11), 4533672H1
<u> </u>	33	88	145668	COLNFET02	145684F6 (COLNFET02), 1456684H1 (COLNFET02), 1456684T6 (COLNFET02), 1992143H1 (CORPNOT02), 2687476F6 (LUNGNOT23), 3139175F6 (SMCCNOT02), 4746319H1 (SMCRUNT01)
	34	68	160291 6	BLADNOT03	3397976X305D2 (UTRSNOT16)
	35	06	169281 6	COLNNOT23	999017R6 (KIDNTUT01), 1342490T1 (COLNTUT03), 1421981F1 (KIDNNOT09), 1692816H1 (COLNNOT23), 2176832F6 (FNDCNOT03), 2451404F6 (FNDCNOT03)
	36	91	196819 1	BRSTNOT04	, 1968191T6 (BRSTNOTO4), 2752967R6 , 3748607H1 (UTRSNOT18)
	37	92	205206 1	LIVRFET02	(HMCINOT01), 027044X1 (S (LIVRFET02), 3931936F6

TABLE 1 (cont.

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	Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone	Library	Fragments
·	æ	93	205620	BEPINOT01	071525F1 (PLACNOBO1), 162720R1 (ADENINBO1), 270498H1 (HNT2NOT01), 1477853T1 (CORPNOT02), 1931058F6 (COLNTUT03), 2056207H1 (BEPINOT01), 2056207X11R1 (BEPINOT01), 2231060F6 (PROSNOT16), 2420063X309D4 (SCORNON02), 3424630H1 (BRSTNOR01), 3873760F6 (HEARNOT06), 3873760T6 (HEARNOT06), SBOA00627D1, SCJA02192V1, SCJA02089V1
<del></del>	39	94	210180 3	BRAITUT02	399584R6 (PITUNOTO2), 399584T6 (PITUNOTO2), 1649058F6 (PROSTUT09), 1902809F6 (OVARNOTO7), 2101803H1 (BRAITUT02), 2101803R6 (BRAITUT02), 3098623H1 (CERVNOTO3)
	40	95	211236	BRAITUT03	(PANCNOT05), 1 1 (BRAITUT03), 1 (ESOGTUN01),
<u>.</u>	41	96	211734 6	BRSTTUT02	487994R6 (HNT2AGT01), 952855R1 (SCORNON01), 952855T1 (SCORNON01), 2117346H1 (BRSTTUT02), 2458342F6 (ENDANOT01), 2731585H1 (OVARTUT04), 3475780H1 (LUNGNOT27), 3538525F6 (SEMANOTOA)
8	42	97	211991	BRSTTUT02	(COLNTUT16), 2794083F6
L	43	86	212345 6	BRSTNOT07	484031H1 (HNT2RAT01), 617559F1 (PGANNOT01), 617559R1 (PGANNOT01), 1575977F1 (LNODNOT03), 2123456H1 (BRSTNOT07), 2958712H1 (ADRENOT09), 3764961H1 (BRSTNOT24)
I	<b>44</b>	66	214879 2	BRAINOT09	1732781F6 (BRSTTUT08), 2050885F6 (LIVRFET02), 2148792H1 (BRAINOT09), 2590822H1 (LUNGNOT22), 2972368T6 (HEAONOT02), SBQA00396D1, SBQA02120D1, SBOA03269D1
	45	100	275194 3	THP1AZS08	1720187X16C1 (BLADNOT06), 2751943H1 (THP1AZS08), 3492378H1 (ADRETUT07)
	46	101	312891	LUNGTUT12	
	47	102	328294 1	HEAONOT05	154741R6 (THP1PLB02), 155904R6 (THP1PLB02), 157816R1 (THP1PLB02), 979920H1 (TONGTUT01), 1233933T6 (LUNGFET03), 1657077F6 (URETTUT01), 2445017F6 (THP1NOT03), 3282941H1 (HEAONOT05), 3341633H1 (SPLNNOT09), 3517140H1 (LUNGNON03)
	48	103	328665 6	HEAONOT05	

TABLE 1 (cont.)

<u> </u>	Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone	Library	Fragments	
	49	104	349080 2	EPIGNOT01	2238441H1 (PANCTUTO2), 2700133F6 (OVARTUT10), 2700133T6 (OVARTUT10), 3490226H1 (EPIGNOT01), 3490802H1 (EPIGNOT01), 4822929H1 (PROSTUT17)	T10), T17)
	50	105	350736 6	CONCNOT01	2130284H1 (KIDNNOT05), 3507366H1 (CONCNOT01), 3557087F6 (LUNGNOT31), 4241774H1 (SYNWDIT01)	T31),
	51	105	357306 0	BRONNOT01	3573060F6 (BRONNOT01), 3573060H1 (BRONNOT01), 3573060T6 (BRONNOT01), 3867263H1 (BRAITUT07), 5013346H1 (BRAXNOT03)	T01),
	52	107	357366 1	BRONNOT01	3028034F6 (HEARFET02), 3152642H1 (ADRENON04), 3573661F6 (BRONNOT01), 3573661H1 (BRONNOT01), 3577568F6 (BRONNOT01)	T01),
	53	108	363342 2	LIVRNOT03	033412R6 (THPINOB01), 074123F1 (THPIPEB01), 263241H1 (HNT2AGT01), 748567R1 (BRAITUT01), 1292088T1 (PGANNOT03), 1517449T1 (PANCTUT01), 3633422H1 (LIVRNOT03)	3),
<u></u>	54	109	399337 7	LUNGNON03	3003233H1 (TLYMNOT06), 3993377H1 (LUNGNON03), 3993377T6 (LUNGNON03), 4251662F6 (BRADDIR01), SBSA02001V1	NO3),
<u></u>	55	110	471793	BRAIHCT02	4717936F6 (BRAIHCT02), 4717936H1 (BRAIHCT02), 4717936T6 (BRAIHCT02)	T02)

### **FABLE 2**

Polypep tide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
Ŋ	562	T29 T43 S76 S142 S165 S202 T214 Y302 S305 Y349 S385 S500 T526 S527		Y235 - D312 PFAM	DNA helicase (GI 531243; SEQ ID NO:113)	BLAST, PFAM, BLOCKS, MOTIFS
9	432	S33 S58 T166 T172 S197 T230 T261 S275 S286 S290 S298 S338 T362 S376 T407 T409		E329 - A355 BLOCKS	CCAAT-box-binding transcription factor	BLOCKS, MOTIFS
7	799	T24 S33 T43 S73 T88 S91 S110 S147 T219 S262 S323 Y380 S532 S586 S756 T795		H250 - H291 Y324 - H346 Y253 - H374 Y380 - H402 PFAM	C2H2-type zinc finger protein (GI 498727)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
æ	137	S3 T38 S74 S75 S118		R85 - L97 PFAM	BTB domain/C2H2-type zinc finger protein	PFAM, PRINTS, MOTIFS
6	230	T178 S187			sirtuin type 3 (GI 5225322)	BLAST, MOTIFS
10	446	T3 S28 S32 T52 T94 T96 S135 S143 T159 T165 S171 S433		H200 - H222 Y228 - H250 Y256 - H278 Y284 - H306	zinc finger protein ZFP113 (GI 5640017)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
11	428	S72 S92 S101 S118 S120 S125 T245 T277 S289 S315 S317 Y326 S409			Skeletal muscle BOP2 (GI 5870834; SEQ ID NO:117)	BLAST, MOTIFS

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tide Seg ID NO:	Amino Acid Residues	Forential Phosphorylation Sites	Forential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
12	290	S45 Y52 T60 S83 S90 T95 T116 T145 T233 T330 S391 S410 S411 T420 T439 T490 S521			Methyl-CpG binding protein (GI 2239126)	BLAST, MOTIFS
13	479	S15 Y29 S30 S118 T173 T183 S203 S217 Y232 S235 T255 S352 S362 Y451		Y232 - H254 H283 - H305 Y311 - H333 Y339 - H361 PFAM	SRE-ZBP (GI 936603)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
14	433	S92 S96 T250 S319 T322 T327 S335 T344		C380 - C421 PFAM	C3HC4-type zinc finger protein	PFAM, BLOCKS,
15	320	T6 S27 T125 T172 S229 S232 T239 S248 S259 S266 Y267 S291			Zinc finger factor (GI 3150148)	MOTIFS BLAST, MOTIFS
16	179	S4			Single-stranded DNA binding protein (csdp) (GI 1562534)	BLAST, MOTIFS
17	494	T73 Y80 S104 Y116 T192 S289 S297 T329 T364 T376 S387		C13 - H41 BLOCKS	Zinc finger transcription factor (GI 2895870)	BLAST, BLOCKS, MOTIFS
98	401	S4 S82 S97 T166 S188 S249 S279 S289 S290 S294 S319 S368 S371 S372 S378 T392 S396		P5 - K81 A114 - S179 G186 - P262 PFAM	HP1-BP74 (GI 1480112)	PFAM, BLOCKS, PRINTS, MOTIFS

Polypep tide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
19	264	S11 S25 S76 S82 S90 S92 S96 S119 T229		F154 - H176 C180 - H202 F208 - H230 Y236 - C259 PFAM	C2H2-type zinc finger protein (GI 429188)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
20	153	T23 S40 T44 S110 S120 T124		R42 - E141 PFAM	High mobility group- like nuclear protein (GI 2822179)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
21	243	S21 S 4 S160 5 S212 9		Y90 - H112 H118 - H140 Y146 - H168 Y174 - H195 PFAM	C2H2-type zinc finger protein (GI 38015)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
22	485	T29 S34 S104 S147 T162 T248 S249 S256 S347 S452 S477		S309 - H331 H337 - H359 Y365 - H387 Y393 - H415 PFAM	BTB domain/C2H2-type zinc finger protein (GI 2843171)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
23	160	S118		C5 - F62 C80 - F137 PFAM	LIM domain protein/CRP2 (GI 487284)	BLAST, PFAM, BLOCKS, PROFILESCAN, MOTIFS
24	511	T36 S 2 T245 9 S405		Y171 - P223 Y267 - K294 BLOCKS	2'-5'oligoadenylate synthetase-related protein p56 (GI 4731857)	BLOCKS, MOTIFS
25	310	S24 S39 T69 Y104 S185 T282 T296	,		SIR2 family transcriptional regulatory protein (GI 2648874)	BLAST, MOTIFS

TABLE 2 (cont.)

							T					_				-						_		~		
Analytical Methods and	Databases BLOCKS,	MOTIFS	MOTIFS BLAST	E	MOTIFS	BLOCKS				MOTIFS	BLAST	BLOCKS	PFAM				MOTIFS	BLAST	BLOCKS	PROFILESCAN		MOTIFS	BLAST.		DEDM	BLOCKS
Identification/ Homologous Sequence		Hiscone procein	Zinc finger protein (q1373394)	1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	cranscription	(94336506)					Zinc finger protein	(9498721)						C3HC4/RING zinc finger	protein (g1321818)		Gimilar to	CCAAT/enhancer-binding	protein (g1947129)			
Signature Sequence(s)	V112 - R134	BLOCKS		Transcription	anti-terminator;	bglG family: E47-1100	C2H2 zinc	fingers:	Y191-H213	Y247-H269	Y275-H297	Y331-H353	Y387-H409	Y415-H437	Y443-H465	Y471-H493		C3HC4 RING	11119CT :	1				bZIP	transcription	factor: P21-P85
Potential Glycosylation Sites							N24 N52 N100	N481								OLIN CCIN	N33 N/9			:				N98 N103		
Potential Phosphorylation Sites	T29 S40 S74 S257	830	T43 S123 T129 S167 S183 S184	S44 Y25 Y98				•	T367 T423 S483	x39 Y44 Y112 Y163						TO 63 05					94 S1	S142 S143 T184 S232 S252 T36 T46	S163	S36 S56 T93 S104		
Amino Acid Residues	331	•	200		100						528							350	, ,			315			120	
Polypep tide Seq ID	NO:		27		28						29							30				31			32	

Polypep tide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
33	326	S59 S38 T207 S284 T319 T43 S80 T137 T155 T211 S238 T239	N209	C2H2 zinc fingers: C143-C171 Y169-H191 F197-H219	Zinc finger protein (g220643)	MOTIFS BLAST PFAM BLOCKS
34	106			Homeobox: R14-K70	CHOX M product; homeobox protein (g62701)	MOTIFS BLAST BLOCKS PFAM PROFILESCAN
35	209	5 T180 3 S201	N18	bZIP transcription factor: K115-E140	geminin (g3219357)	MOTIFS BLAST PFAM
36	212	S107 S45 Y35	N92	HMG box: M1-Q36	Smarcel-related protein (GI 4321968)	MOTIFS BLAST PFAM
37	359	T329 T50 S125 S224 S230 S235 S344 S31 S215 S312 Y42	N45 N340	C2H2 zinc fingers: F278-C306 Y304-H328 F334-H356	BKLF; CACCC-box binding protein (g1244515)	MOTIFS BLAST BLOCKS PFAM
38	445	S68 T87 S153 S339 S405 S55 T105 S315 S422 Y419	N337 N374 N388	C3HC4 RING fingers: C74-P120 N228-C235	ARI (RING finger) protein (g2058299)	MOTIFS BLAST BLOCKS PFAM
39	433	S283 T44 T57 T123 S136 T185 T220 S239 T268 S313 S330 T105 T109 S125 T216	N169 N206		skm-BOP2 zinc finger protein (g1809327)	MOTIFS BLAST

Analytical Methods and Databases	MOTIFS BLAST	MOTIFS BLAST BLOCKS PFAM PROFILESCAN	MOTIFS BLOCKS PFAM	MOTIFS BLAST PFAM	MOTIFS BLAST PFAM BLOCKS	MOTIFS BLAST
Identification/ Homologous Sequence	Sir2 family protein (g5353746)	ADA2 transcriptional adaptor protein (g170991)		Sry-related protein (g211510)	C2H2 zinc finger protein (g5757625)	Transcriptional regulator (g2621798)
Signature Sequence(s)	,	Myb-like DNA binding domain: D72-F118	mutT domain: V29-L70	НМG box: M1-Q36	C2H2 zinc fingers: H230-H252 Y258-H280 Y286-H308 Y314-H336 Y342-H364 F370-H392 Y398-H420 Y426-H448	
Potential Glycosylation Sites	N308 N324	N366 N425	N117		N465	
Potential Phosphorylation Sites	T72 T84 T184 S191 T244 S88 T162 T229 T294 S330	T76 T106 S148 T309 S12 T253 S299 S357 T373 T427 Y61 Y114	S37 T55 T64 S83 S22 Y146	S79 S127 T12 T45	T15 S24 S66 S83 T97 T105 T109 S128 T149 S153 S198 T203 T225 T238 T296 S466 Y258	T59 S112 S120 S100 S139 Y64
Amino Acid Residues	355	443	164	215	539	182
Polypep tide Seg ID NO:	40	41	42	43	24 44	45

Procential Procession							
Seq ID         Acid         Sites         Sequence (s)           NO:         \$494 \$31 \$44 \$117         N29 N39 N250         C2H2 zinc           1123 \$185 \$216         N351         Y285-H307         Y31-H335           46         \$234         T489 Y76 Y285         Y31-H335         Y31-H335           47         \$206         T489 Y76 Y285         Y44 N177         Y453-H47           48         \$172         T5 S87 S40 S45 S46         N44 N177         Myc-type HLH domain:           49         \$275         T124 S22 T64         X200 N14 N26         Y228-H307           50         \$236         T189 T217 Y256         Y200 N214 N238         C2H2 zinc           \$118         \$113         \$116         N260         \$1108-R160           \$118         \$126 S17 Y256         Y228-H350         Y228-H350           \$1         \$125 S42 T167         Y000-H222         Y228-H350           \$1         \$125 S42 T167         N40         C3HC4 R1NG           \$1         \$215 S42 T167         N40         C1100-H222           \$1         \$125 S42 T167         N40         C1100-H222           \$1         \$124 S191 T31 S41         Y113-E134           \$1         \$124 S154 S191 T31 S41 <td>  Folypep   tide</td> <td>Amino</td> <td>  Potential   Phosphorvlation</td> <td>Potential Glycosylation</td> <td>Q; quature</td> <td>Thout if fination /</td> <td>Analytical</td>	Folypep   tide	Amino	Potential   Phosphorvlation	Potential Glycosylation	Q; quature	Thout if fination /	Analytical
46 534 T489 Y76 Y285 47 206 S10 S14 S215 48 172 S18 S216 49 534 T489 Y76 Y285 40 S293 S321 S409 40 S294 S311 T249 4131-H363 42 S211 T249 43 S295 S213 S409 44 S26 S16 S26 S16 47 206 S10 S144 S26 48 172 T5 S87 S96 S115 49 275 T124 S22 T64 49 275 S15 S42 T167 50 S36 S15 S42 T167 50 S36 S15 S42 T167 50 S36 S15 S42 T167 51 S28 S116 T127 52 S15 S48 S116 T127 52 S15 S48 S116 T127 53 S16 S116 T127 54 S116 T127 55 S17 S48 S116 T127 56 S116 T127 57 S88 S116 T127 58 S116 T127 58 S116 T127 59 S118 T139 T31 S41 50 Chromodomain: 51 S12 S13 S118 T131 S41 51 S13 S13 S13 S41 51 S13 S41 51 S13 S41 S41 51 S13 S41 S41 51 S13 S41 51 S13 S41 51 S13 S41 51 S41 S41 S41 51 S41 S41 S41 51 S41 S41 S41	Seq ID NO:	Acid Residues	Sites	Sites	Seguence (s)	Homologous Sequence	Methods and Databases
46 534 T123 S185 S216 N351 fingers: S476 S504 S176 S204 S176 S204 S176 S204 S176 S204 S176 S204 S176 S204 S176 S205 S21 T249 S21 T249 S20			S31	N39	C2H2 zinc		
46 534 T489 Y76 Y285 Y313-H335 Y313-H335 S293 S323 S409 Y76 Y285 Y313-H353 C369-H391 Y411-H363 C369-H391 Y425-H447 Y426-H247 Y			S185	N351	fingers:		
46 534 T489 Y76 Y285 S323 S409 C369-H391 C369-			S504		Y285-H307		
46 534 T489 Y76 Y285 C369-H363 C369-H361 Y341-H363 C369-H391 Y425-H447 Y425-H475 Y481-H503 Y509-H531 C210 S144 S26 S107 T148 S185 S107 T148 S185 S107 T148 S185 S107 T148 S185 S107 T124 S22 T64 S115 S118 T139 T161 S118 T131 S41 S118			<b>S211</b>		X313-H335		
46 534 T489 Y76 Y285 C369-H391 Y397-H419 Y425-H447 Y425-H447 Y481-H503 Y206 S144 S26 S100 S144 S26 S107 T148 S185 Y209-H531 Y208-H503 Y209-H531 Y208-H148 Y208-H503 Y209-H531 Y208-H169 Y209-H531 Y208-H169 Y209-H531 Y208-H169 Y209-H531 X481-H503 X4			<b>S</b> 323		Y341-H363		MOTIFS
47 206 S17 S40 S45 S46 N44 N177 Myc-type HLH domain: 48 172 T124 S22 T64 49 275 T189 T217 Y256 50 236 S156 S116 T127 51 214 S185 S14 S181 N40 C38C C38C H194 52 215 T22 T81 Y213 51 214 S151 S191 T31 S41 51 214 S151 S191 T31 S41 51 214 S151 S191 T31 S41	46	534	¥76		C369-H391	Zinc ringer protein	BLAST
47 25 S7 S40 S45 S46 N44 N177 N459-H475 S100 S144 S26 S107 T148 S185 O188 S100 S144 S26 S107 T148 S185 O188-R160 O188-R161 O189-R161 O18					Y397-H419	(g13/3394)	PFAM
48 172 T148 S185					Y425-H447		BLOCKS
48 172 T148 S185 N40 N214 N217 Myc-type HLH domain: Y38 T206 S107 T148 S185  48 172 T5 S87 S96 S115 T124 S22 T64 S185 S14 S48 T54 N210 N214 N238 C2H2 zinc fingers: T189 T217 Y256 S16 T167 S28 S16 T167 S185 S18					Y453-H475		
47 206 \$10 \$144 \$26   M44 N177   Myc-type HLH domain:  48 172 T5 \$87 \$96 \$115   Q108-R160    49 275 T189 T217 Y256   Y228-H250    50 236 T222 T81 Y213   S156 S115   T124 S18 S116 T127    51 214 \$21 T31 T31 T31 T31 T31 T31 T31 T31 T31 T3					Y481-H503		
47 206 \$10 \$144 \$26					Y509-H531		
47 206 \$100 \$144 \$26   domain: Y38  48 172 T148 \$185  49 275 T189 T217 Y256  50 236 T222 T64   N20 N214 N238 C2H2 zinc F172-H194 Y200-H222 Y228-H250  51 214 \$154 \$191 T31 \$41  51 214 \$154 \$191 T31 \$41  52 20 214 \$1204   N216 N216   Chromodomain: Y20 S10 Y20 S10 Y213			S45	N44 N177			MOTIFS
47 206 S107 T148 S185 domain:  48 172 T5 S87 S96 S115  49 275 T189 T217 Y256  50 236 T222 T61  51 214 S18 S116 T127  52	!				Myc-type HLH		BLAST
48 172 T5 S87 S96 S115 49 275 T189 T217 Y256 50 236 T22 T81 Y213 518 T124 S22 T64  S185 S14 S48 T54 N210 N214 N238 C2H2 Zinc fingers: F172-H194 Y200-H222 Y200-H222 Y228-H250 S157 S42 T167 N40 C3HC4 RING finger: P122 T81 Y213  51 214 S154 S191 T31 S41 V113-E134		206	7 T148		domain:	Musculin (g3599519)	PFAM
172   T5 S87 S96 S115   T124 S22 T64   N210 N214 N238   C2H2 zinc S118 T139 T161   N260   F172-H194   Y200-H222   Y200-H222   Y228-H250   S157 S42 T167   N40   Finger: P126-L150   S7 S8 S116 T127   N2   Chromodomain: V113-E134   V113-E134   V113-E134   S154 S191 T31 S41   S154 S191 T31 S41   S154 S191 T31 S41   S154 S194   S154 S191 T31 S41   S154 S194   S154 S194 S195   S154 S194 S195   S154 S194 S195 S195 S195 S195 S195 S195 S195 S195			Y38		Q108-R160		BLOCKS
172   T5 S87 S96 S115   T124 S22 T64   S185 S14 S48 T54   N210 N214 N238   C2H2 zinc     275   T189 T217 Y256   F172-H194     275   T189 T217 Y256   F172-H194   Y200-H222     236   S157 S42 T167   N40   Einger:     236   T222 T81 Y213   P126-L150     214   S154 S191 T31 S41   T204   T204     214   S154 S191 T31 S41   T204   T204     215   T204   T205 T81 T31 S41   T204   T205 T81 T31 S41     215   T205 T81 T31 S41   T205 T81 T31 T31 T31 S41   T205 T81 T31 T31 S41   T205 T81 T31 T31 S41   T205 T81 T31 T31 T31 S41   T205							PROFILESCAN
T124 S22 T64   S185 S14 S48 T54   N210 N214 N238   C2H2 zinc     S185 S14 S48 T54   N210 N214 N238   C2H2 zinc     S118 T139 T161   N260   F172-H194     Y200-H222   Y200-H222     Y228-H250   S157 S42 T167   N40   C3HC4 RING     T222 T81 Y213   F126-L150     S7 S8 S116 T127   N2   Chromodomain:     S154 S191 T31 S41   T204   V113-E134     T204   T204   C3HC4 C13   C1	48	172	T5 S87 S96 S115			KRAB zinc finger	MOTIFS
S185 S14 S48 T54   N210 N214 N238   C2H2 zinc     S118 T139 T161   N260   fingers:     T189 T217 Y256   Y200-H222   Y200-H222     S157 S42 T167   N40   C3HC4 RING     T222 T81 Y213   Finger:   P126-L150     S7 S8 S116 T127   N2   Chromodomain:     T204   T204   T31 S41   T31 S41   T204   T31 S41     T204   T204   T31 S41   T31 S41   T31 S41   T31 S41   T31 S41     S154 S191 T31 S41	2		S22			protein (g1049295)	BLAST
275 T189 T161 N260 fingers:			S14	N210 N214 N238	C2H2 zinc		000
275 T189 T217 Y256 F172-H194 Y200-H222 Y228-H250 S157 S42 T167 N40 C3HC4 RING finger:			T139	N260	fingers:	Repressor	MOTIFS
236 S157 S42 T167 N40 C3HC4 RING finger: P122 T81 Y213 S7 S8 S116 T127 N2 Chromodomain: 214 S154 S191 T31 S41 C13-E134	49	275	T217		F172-H194	transcriptional factor	BLAST
236 S157 S42 T167 N40 C3HC4 RING finger: P122 T81 Y213 Finger: P126-L150 S7 S8 S116 T127 N2 Chromodomain: T204 T1204 V113-E134					Y200-H222	(g1017722)	PFAM
236 T167 N40 C3HC4 RING 1222 T81 Y213 finger: S7 S8 S116 T127 N2 Chromodomain: 214 S154 S191 T31 S41 Chromodomain: T204 V113-E134					Y228-H250		BLOCKS
236 T222 T81 Y213 finger:			S42	N40	C3HC4 RING		MOTIFS
214 S154 S191 T31 S41 Chromodomain: V113-E134	20	236	T81		finger:	Arladne-2 KING iinger	BLAST
214 S154 S191 T31 S41 Chromodomain: T204					P126-L150	protein (g3445441)	BLOCKS
214 S154 S191 T31 S41 ULIONNOQOMAIN: T204 V113-E134			S11	N2	1000		MOTIFS
	51	214	S191		V113-E134	Nucleoplasmin (d833629)	BLAST
			1.204			, , , , , , , , , , , , , , , , , , , ,	BLOCKS

Polypep tide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
52	396	T348 T392 S118 T193 T201 S270 S294 S80 S112 S206 S260 T313 T355 S375 S387	N2	C3HC4 RING finger: C26-C50	Midline 1/ cerebellar isoform 1 RING finger protein (g3462503)	MOTIFS BLAST PFAM BLOCKS PROFILESCAN
53	486	S29 T58 S155 S239 T292 T379 S146 T271 S425			5'-nucleotidase (g633071)	MOTIFS BLAST
54	555	S432 T502 S68 S195 T199 T226 S315 T379 T441 T534 S170 S248 S282 S291 T327 T336 S391 S422 T481 Y257 Y274	N25 N66 N246 N364	ATP/GTP binding site (P-loop): A434-T441	Transcription termination factor I (TTF-I) interacting peptide 5 isoform (g2183083)	MOTIFS BLAST
55	61	T34 T42 Y48			Putative leucine-rich DNA-binding protein (9555991)	MOTIFS BLAST

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Nucleotide Seq ID NO:	Selected Fragment	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
56	169-215	Reproductive (0.224) Nervous (0.198) Cardiovascular (0.112)	Cell Proliferative (0.725) Inflammation (0.190)	PBLUESCRIPT
57	551-595	Hematopoietic/Immune (0.240) Reproductive (0.180) Gastrointestinal (0.120)	Cell Proliferative (0.700) Inflammation (0.360)	PBLUESCRIPT
58	541-585	Nervous (0.286) Reproductive (0.286) Cardiovascular (0.214)	Cell Proliferative (0.643) Trauma (0.214)	PBLUESCRIPT
59	109-153	Reproductive (1.000)	Cell Proliferative (1.000) Inflammation (1.000)	PBLUESCRIPT
09	435-479	Hematopoietic/Immune (0.211) Gastrointestinal (0.183) Reproductive (0.183)	Cell Proliferative (0.620) Inflammation (0.338)	PBLUESCRIPT
61	1195-1239	Reproductive (0.248) Cardiovascular (0.174) Nervous (0.157)	Cell Proliferative (0.637) Inflammation (0.256)	PBLUESCRIPT
62	217-261	Reproductive (0.429) Nervous (0.238) Cardiovascular (0.095)	Cell Proliferative (0.667) Inflammation (0.143) Trauma (0.095)	PBLUESCRIPT
63	919-963	Reproductive (0.265) Nervous (0.235) Cardiovascular (0.088)	Cell Proliferative (0.618) Inflammation (0.206)	PSPORT1
64	823-876	Reproductive (0.382) Nervous (0.176) Gastrointestinal (0.118)	Cell Proliferative (0.794)	PSPORT1
65	380-424	Reproductive (0.346) Nervous (0.154) Gastrointestinal (0.135)	Cell Proliferative (0.750) Inflammation (0.231)	PSPORT1

		TABLE 3 (cont.)		
eotide ID NO:	Selected Fragment	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
99	757-801	Nervous (0.222) Hematopoietic/Immune (0.167) Reproductive (0.167)	Cell Proliferative (0.778) Inflammation (0.222)	pincy
67	812-856	Reproductive (0.246) Nervous (0.180) Gastrointestinal (0.148)	Cell Proliferative (0.639) Inflammation (0.246)	pINCY
89	326-370	Reproductive (0.500) Nervous (0.200) Gastrointestinal (0.150)	Cell Proliferative (0.700) Trauma (0.150)	pincy
69	703-747	Reproductive (0.278) Hematopoietic/Immune (0.204) Nervous (0.148)	Cell Proliferative (0.777) Inflammation (0.222)	pincy
70	759~803	Reproductive (0.261) Gastrointestinal (0.217) Nervous (0.174)	Cell Proliferative (0.565) Trauma (0.130)	pincy
71	110-154	Nervous (0.250) Developmental (0.208) Gastrointestinal (0.167)	Cell Proliferative (0.583) Trauma (0.167)	pincy
72	529-573	Reproductive (0.186) Gastrointestinal (0.168) Hematopoietic/Immune (0.138)	Cell Proliferative (0.700) Inflammation (0.251)	PINCY
73	1784-1828	Reproductive (0.286) Hematopoietic/Immune (0.190) Nervous (0.167)	Cell Proliferative (0.667) Inflammation (0.286)	PSPORT1
74	111-155	Reproductive (0.316) Nervous (0.211) Hematopoietic/Immune (0.158)	Cell Proliferative (0.632) Inflammation (0.211)	PSPORT1
75	543-587	Reproductive (0.258) Nervous (0.206) Gastrointestinal (0.134)	Cell Proliferative (0.608) Inflammation (0.196)	pincy

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		(June 5) (Court.)		
Nucleotide	Selected Fragment	Tissue Expression	Disease or Condition	
Seq ID NO:		(Fraction of Total)	(Fraction of Total)	Vector
	272-316	Reproductive (0.246)	Cell Proliferative	
16	-	Nervous (0.180)	(0.606) Inflammation	PINCY
		Hematopoietic/Immune (0.148)	(0.279)	•
	227-271	Hematopoietic/Immune (0.222)	Cell Proliferative	
77		Endocrine (0.167)	(0.666) Inflammation	PINCY
		Cardiovascular (0.111)	(0.333)	•
	487-531	Gastrointestinal (0.375)	Cell Proliferative	
80/		Reproductive (0.250)	(0.500)	PINCY
			Intlammation (0.250)	
	111-155	Gastrointestinal (0.280)	Cell Proliferative	
79		Hematopoietic/Immune (0.240)	(0.640) Inflammation	PINCY
		Reproductive (0.120)	(0.440)	i
	595-639	Reproductive (0.211)	Cell Proliferative	
80		Gastrointestinal (0.158)	(0.684) Inflammation	PINCY
7		Urologic (0.158)	(0.263)	·
	425-469	Reproductive (0.222)	Cell Proliferative	4
81		Gastrointestinal (0.160)	(0.568) Inflammation	PSPORTI
		Nervous (0.148)	(0.259)	
	774-818	Gastrointestinal (0.200)	Cancer (0.600) Trauma	
82		Hematopoietic/Immune (0.200)	(0.200) Inflammation	PBLUESCRIPT
		Nervous (0.200)	(0.200)	
	517~561	Nervous (0.526)	Cancer (0.342) Fetal	
83		Reproductive (0.132)	(0.158) Inflammation	PBLUESCRIPT
		Cardiovascular (0.105)	(0.158)	
	1944-1988	Nervous (0.250)		
84		Reproductive (0.188)	Cancer (0.438) Fecal	PSPORT1
		Endocrine (0.125)	(0.230) Itauma (0.230)	
	1027-1071	Reproductive (0.219)	Cancer (0.458)	
·85		Nervous (0.206)	Inflammation (0.232)	PSPORT1
		Hematopoietic/Immune (0.116)	Fetal (0.181)	

Vector

PT7T3

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Nucleotide Se Seq ID NO:		IABLE 3 (cont.)	
98	Selected Fragment	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)
	658-702	Reproductive (0.227) Hematopoietic/Immune (0.182) Gastrointestinal (0.167)	Cancer (0.424) Inflammation (0.318) Fetal (0.167)
87	488-532	Nervous (0.200) Reproductive (0.200) Musculoskeletal (0.120)	Cancer (0.320) Fetal (0.320) Inflammation (0.320)
88	379-423	· ·	Cancer (0.417) Fetal (0.167) Neurological (0.167)
89	632-676	Reproductive (0.417) Cardiovascular (0.167) Gastrointestinal (0.167)	Cancer (0.333) Fetal (0.167) Inflammation (0.167)
06	258-302	Reproductive (0.294) Nervous (0.137) Hematopoietic/Immune (0.118)	Cancer (0.569) Fetal (0.431) Inflammation (0.176)
91	433-477	Reproductive (0.750) Nervous (0.250)	
92	542-586	Gastrointestinal (0.273) Hematopoietic/Immune (0.273) Developmental (0.182)	Cancer (0.455) Inflammation (0.364) Fetal (0.182)
93	218-262	Reproductive (0.272) Nervous (0.204) Cardiovascular (0.126)	Cancer (0.447) Inflammation (0.214) Fetal (0.155)
94	541-585	Reproductive (0.273) Nervous (0.250) Cardiovascular (0.159)	Cancer (0.364) Fetal (0.205) Inflammation (0.205)
95	111-155	Reproductive (0.250) Gastrointestinal (0.173) Nervous (0.154)	9
96	597-641	Reproductive (0.261) Cardiovascular (0.217) Nervous (0.130)	

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Nucleotide Seg ID NO:	Selected Fragment	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
0	434-478	Cardiovascular (0.222)	Cancer (0.667)	
'n	•	Endocrine (0.222) Gastrointestina] (0.222)	Fetal (0.111)	PSPORT1
	218-247	Reproductive (0.333)	Cancer (0.559)	
86	920-964	Gastrointestinal (0.129)	Inflammation (0.204)	DINCY
		Hematopoietic/Immune (0.118)	Fetal (0.183)	
	327-371	Gastrointestinal (0.211)	Cancer (0.421)	
66		Reproductive (0.211)	Fetal (0.316)	DINCY
		Cardiovascular (0.158)	Inflammation (0.158)	4
	596-625	Reproductive (0.230)	Cancer (0.590)	
100		Nervous (0.164)	Inflammation (0.246)	PSPORT
		Gastrointestinal (0.131)		
	487-531	Cardiovascular (0.235)	Cancer (0.588)	
101		Reproductive (0.235)	Inflammation (0.176)	DINCY
73		Hematopoietic/Immune (0.176)	Trauma (0.118)	
	218-247	Gastrointestinal (0.241)	Cancer (0.448)	
102	542-586	Hematopoietic/Immune (0.207)	Fetal (0.276)	DINCY
		Cardiovascular (0.138)	Inflammation (0.276)	•
	219-263	Reproductive (0.500)	Cancer (0.500)	
103		Cardiovascular (0.250)	Inflammation (0.250)	DINCY
		Hematopoietic/Immune (0.250)	Trauma (0.250)	ŀ
	111-140	Hematopoietic/Immune (0.286)	Cancer (0.333)	
104	327-371	Nervous (0.238)	Fetal (0.286)	DINCY
		Reproductive (0.143)	Inflammation (0.286)	4
	243-281	Musculoskeletal (0.286)	Inflammation (0.429)	
105		Nervous (0.286)	Fetal (0.286)	DINCY
		Gastrointestinal (0.143)	Cancer (0.286)	
	271-315	Nervous (0.800)	Cancer (0.400)	
106		Reproductive (0.100)	Inflammation (0.200)	PINCY
		Cardiovascular (0.100)	Trauma (0.200)	

	Vector	pincy	DINCY	PSPORT1	pincy
	Disease or Condition (Fraction of Total)	Cancer (0.273) Trauma (0.273) Inflammation (0.182)	Cancer (0.465) Fetal (0.291) Inflammation (0.186)	Inflammation (0.417) Cancer (0.333) Trauma (0.167)	Neurological (1.000)
TABLE 3 (cont.)	Tissue Expression (Fraction of Total)	Cardiovascular (0.364) Gastrointestinal (0.182) Reproductive (0.182)	Nervous (0.256) Reproductive (0.256) Hematopoietic/Immune (0.128)	Cardiovascular (0.250) Hematopoietic/Immune (0.250) Nervous (0.167)	Nervous (1.000)
	Selected Fragment	489-533	156-200	1459-1503	164-208
	Nucleotide Seq ID NO:	107	108	109	110

# TABLE

Nucleotide SEQ ID No:	le Library	Library Comment
56	SPLNFET0 1	Library was constructed at Stratagene, using RNA isolated from a pool of fetal spleen tissue. Following vector packaging, $2 \times 10^6$ primary clones were then amplified to stabilize the library for long-term storage. Amplification may significantly skew sequence abundances.
57	SYNORAB0 1	Library was constructed using RNA isolated from the synovial membrane tissue of a 68-year-old Caucasian female with rheumatoid arthritis.
58	KIDNNOT0 1	ary was asian fe
65	PLACNOB0	Library was constructed using RNA isolated from placenta.
09	HNT2RATO 1	Library was constructed at Stratagene (STR937231), using RNA isolated from the hNT2 cell line (derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor). Cells were treated with retinoic acid for 24 hours.
75	EOSIHETO 2	Library was constructed using RNA isolated from peripheral blood cells apheresed from a 48-year-old Caucasian male. Patient history included hypereosinophilia. The cell population was determined to be greater than 77% eosinophils by Wright's staining.
62	HNT2AGT0 1	Library was constructed at Stratagene (STR937233), using RNA isolated from the hNT2 cell line (derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor). Cells were treated with retinoic acid for 5 weeks and with mitotic inhibitors for two weeks and allowed to mature for an additional 4 weeks in conditioned medium.
63	PROSNOTO 2	Library was constructed using RNA isolated from the diseased prostate tissue removed from a 50-year-old Caucasian male during a retropubic prostatectomy. Pathology indicated adenofibromatous hyperplasia was present. Pathology for the associated tumor tissue indicated adenocarcinoma Gleason grade 3+3. Patient history included dysuria, carcinoma in situ of prostate, coronary atherosclerosis, and hyperlipidemia.
64	COLNTUTO 2	Library was constructed using RNA isolated from colon tumor tissue removed from a 75-year-old Caucasian male during a hemicolectomy. Pathology indicated invasive grade 3 adenocarcinoma arising in a tubulovillous adenoma, which was distal to the ileocecal valve in the cecum. The tumor penetrated deeply into the muscularis propria but not through it.

# TABLE 4 (cont.)

	Nucleotide SEO ID NO:	Library	Library Comment
		KIDNTUT0 1	Library was constructed using RNA isolated from the kidney tumor tissue removed from an 8-month-old female during nephroureterectomy. Pathology indicated Wilms' tumor (nephroblastoma), which involved 90 percent of the renal parenchyma. Prior to surgery, the patient was receiving heparin anticoagulant therapy.
	99	THYRNOT0	Library was constructed using RNA isolated from thyroid tissue removed from the left thyroid of a 28-year-old Caucasian female during a complete thyroidectomy. Pathology indicated a small nodule of adenomatous hyperplasia present in the left thyroid. Pathology for the associated tumor tissue indicated dominant follicular adenoma, forming a well-encapsulated mass in the left thyroid.
7	67	BLADTUT0 4	Library was constructed using RNA isolated from bladder tumor tissue removed from a 60-year-old Caucasian male during a radical cystectomy, prostatectomy, and vasectomy. Pathology indicated grade 3 transitional cell carcinoma in the left bladder wall. Carcinoma in-situ was identified in the dome and trigone. Patient history included tobacco use. Family history included type I diabetes, a malignant neoplasm of the stomach, atherosclerotic coronary artery disease, and an acute myocardial infarction.
6	68	PROSNOT1 5	Library was constructed using RNA isolated from diseased prostate tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 2+3). The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer, secondary bone cancer, and benign hypertension.
	69	BRSTTUTO 8	Library was constructed using RNA isolated from breast tumor tissue removed from a 45-year-old Caucasian female during unilateral extended simple mastectomy. Pathology indicated invasive nuclear grade 2-3 adenocarcinoma, ductal type, with 3 of 23 lymph nodes positive for metastatic disease. Greater than 50% of the tumor volume was in situ, both comedo and non-comedo types. Immunostains were positive for estrogen/progesterone receptors, and uninvolved tissue showed proliferative changes. The patient concurrently underwent a total abdominal hysterectomy. Patient history included valvuloplasty of mitral valve without replacement, rheumatic mitral insufficiency, and rheumatic heart disease. Family history included acute myocardial infarction, atherosclerotic coronary artery disease, and type II diabetes.

Ļ	Nucleotide SEQ ID NO:	Library	Library Comment
L	70	PROSNOT1 9	Library was constructed using RNA isolated from diseased prostate tissue removed from a 59-year-old Caucasian male during a radical prostatectomy with regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 3+3). The patient presented with elevated prostate-specific antigen (PSA). Patient history included colon diverticuli, asbestosis, and thrombophlebitis. Previous surgeries included a partial colectomy. Family history included benign hypertension, multiple myeloma, hyperlipidemia and rheumatoid arthritis.
	71	THP1NOT0	Library was constructed using RNA isolated from untreated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
7	72	THP1NOT0	Library was constructed using RNA isolated from untreated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
<u></u>	73	HIPOAZTO 1	Library was constructed from RNA isolated from diseased hippocampus tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.
	74	HIPOAZTO 1	Library was constructed from RNA isolated from diseased hippocampus tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease
	75	BRSTNOT1 3	Library was constructed using RNA isolated from breast tissue removed from the left medial lateral breast of a 36-year-old Caucasian female during bilateral simple mastectomy and total breast reconstruction. Pathology indicated benign breast tissue. Patient history included a breast neoplasm, depressive disorder, hyperlipidemia, chronic stomach ulcer, and an ectopic pregnancy. Family history included myocardial infarction, cerebrovascular disease, atherosclerotic coronary artery disease, hyperlipidemia, skin cancer, breast cancer, depressive disorder, esophageal cancer, bone cancer, Hodgkin's lymphoma, bladder cancer, and heart condition.
<u></u>	76	NPOLNOTO 1	Library was constructed using RNA isolated from nasal polyp tissue removed from a 78-year-old Caucasian male during a nasal polypectomy. Pathology indicated a nasal polyp and striking eosinophilia. Patient history included asthma and nasal polyps.

# TABLE 4 (cont.)

<u> </u>	Nucleotide SEQ ID NO:	Library	Library Comment
	77	ADRENOTO 9	Library was constructed using RNA isolated from left adrenal gland tissue removed from a 43-year-old Caucasian male during nephroureterectomy, regional lymph node excision, and unilateral left adrenalectomy. Pathology indicated no diagnostic abnormalities of the adrenal gland. Pathology for the associated tumor tissue indicated a grade 2 renal cell carcinoma mass in the posterior lower pole of the left kidney with invasion into the renal pelvis.
	78	SPLNNOT1 1	Library was constructed using RNA isolated from diseased spleen tissue removed from a 14-year-old Asian male during a total splenectomy. Pathology indicated changes consistent with idiopathic thrombocytopenic purpura. The patient presented with bruising.
78	79	CONCNOT0 1	Library was constructed using RNA isolated from chest wall soft tissue removed from a 63-year-old Caucasian male during a chest wall lesion destruction. Pathology indicated surgical margins were free of tumor. Pathology for the associated tumor tissue indicated invasive grade 3 adenocarcinoma, forming a mass that extended through the visceral pleura to involve parietal pleura. Patient history included MEN (multiple endocrine neoplasia) syndrome type I, abnormal secretion of gastrin, alcohol and tobacco abuse, calcium metabolism disease, chronic stomach ulcer with hemorrhage, lung cancer, and calculus of the kidney. Family history included prostate cancer, benign hypertension, stroke, atherosclerotic coronary artery disease, type II diabetes, hyperlipidemia, and cancer of an unspecified location.
	80	TONSNOT0	Library was constructed using RNA isolated from diseased left tonsil tissue removed from a 6-year-old Caucasian male during adenotonsillectomy. Pathology indicated reactive lymphoid hyperplasia, bilaterally. Family history included benign hypertension, myocardial infarction, and atherosclerotic coronary artery disease.
	81	LUNGNON0 3	This normalized library was constructed from 2.56 x 10 <sup>6</sup> independent clones from a lung tissue library. RNA was made from lung tissue removed from the left lobe a 58-year-old Caucasian male during a segmental lung resection. Pathology for the associated tumor tissue indicated a metastatic grade 3 (of 4) osteosarcoma. Patient history included soft tissue cancer, secondary cancer of the lung, prostate cancer, and an acute duodenal ulcer with hemorrhage. Patient also received radiation therapy to the retroperitoneum. Family history included prostate cancer, breast cancer, and acute leukemia. The normalization and hybridization conditions were adapted from Soares et al., PNAS (1994) 91:9228; Swaroop et al., NAR (1991) 19:1954; and Bonaldo et al., Genome Research (1996) 6:791.

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	Nucleotide SEQ ID NO:	Library	Library Comment
L	82	BMARNOT0 2	The library was constructed using Clontech RNA isolated from the bone marrow of 24 male and female Caucasian donors, 16 to 70 years old.
	83	SINTNOTO 2	The library was constructed using RNA isolated from the small intestine of a 55-year-old Caucasian female, who died from a subarachnoid hemorrhage. Serologies were positive for cytomegalovirus (CMV),
	84	CRBLNOT0 1	libra -old
	85	BRSTNOT0 3	The library was constructed using RNA isolated from diseased breast tissue removed from a 54-year-old Caucasian female during a bilateral radical mastectomy.  Pathology for the associated tumor tissue indicated residual invasive grade 3 mammary ductal adenocarcinoma. Patient history included kidney infection and condyloma acuminatum. Family history included benign hypertension, hyperlipidemia and a malignant neoplasm of the colon.
79	98	BEPINONO 1	The normalized bronchial epithelium library was constructed from 5.12 million independent clones from a bronchial epithelium library. RNA was isolated from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male. The normalization and hybridization conditions were adapted from Soares et al., PNAS (1994) 91:9228, using a 24-hour reannealing hybridization period
	87	THYRNOT0 3	The library was constructed using RNA isolated from thyroid tissue removed from the left thyroid of a 28-year-old Caucasian female during a complete thyroidectomy. Pathology indicated a small nodule of adenomatous hyperplasia present in the left thyroid. Pathology for the associated tumor tissue indicated dominant follicular adenoma, forming a well-encapsulated mass in the left thyroid.
	88	COLNFET0 2	The library was constructed using RNA isolated from the colon tissue of a Caucasian female fetus who died at 20 weeks' gestation.
	89	BLADNOT0 3	The library was constructed using RNA isolated from bladder tissue removed from an 80-year-old Caucasian female during a radical cystectomy and lymph node excision. Pathology for the associated tumor tissue indicated grade 3 invasive transitional cell carcinoma. Patient history included malignant neoplasm of the uterus, atherosclerosis, and atrial fibrillation. Family history included acute renal failure, osteoarthritis, and atherosclerosis.

# **FABLE 4 (cont.**

Nucleotide SEQ ID NO:	Library	Library Comment
06	COLNNOT2 3	The library was constructed using RNA isolated from diseased colon tissue removed from a 16-year-old Caucasian male during a total colectomy with abdominal/perineal resection. Pathology indicated gastritis and pancolonitis consistent with the acute phase of ulcerative colitis. Inflammation was more severe in the transverse colon with inflammation confined to the mucosa. The ascending and sigmoid colon was mildly involved. Family history included irritable bowel syndrome.
91	BRSTNOTO	constructed using RNA isolian female during a unile associated tumor tissue it history included benigr history included cerebrand liver cancer.
92	LIVRFETO 2	The library was constructed using RNA isolated from liver tissue removed from a Caucasian female fetus who died at 20 weeks' gestation. Family history included seven days of erythromycin treatment for bronchitis in the mother during the first trimester.
93	BEPINOTO 1	The library was constructed using RNA isolated from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male.
94	BRAITUTO 2	The library was constructed using RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Family history included a malignant neoplasm of the kidney.
95	BRAITUTO 3	The library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe a 17-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated a grade 4 fibrillary giant and small-cell astrocytoma. Family history included benign hypertension and cerebrovascular disease.
96	BRSTTUTO 2	The library was constructed using RNA isolated from breast tumor tissue removed from a 54-year-old Caucasian female during a bilateral radical mastectomy with reconstruction. Pathology indicated residual invasive grade 3 mammary ductal adenocarcinoma. The remaining breast parenchyma exhibited proliferative fibrocystic changes without atypia. One of 10 axillary lymph nodes had metastatic tumor. Patient history included kidney infection and condyloma acuminatum. Family history included benign hypertension, hyperlipidemia, and a malignant colon neoplasm.

# TABLE 4 (cont.)

L			
	SEQ ID NO:	Library	Library Comment
	97	BRSTTUTO 2	The library was constructed using RNA isolated from breast tumor tissue removed from a 54-year-old Caucasian female during a bilateral radical mastectomy with reconstruction. Pathology indicated residual invasive grade 3 mammary ductal adenocarcinoma. The remaining breast parenchyma exhibited proliferative fibrocystic changes without atypia. One of 10 axillary lymph nodes had metastatic tumor. Patient history included kidney infection and condyloma acuminatum. Family history included benign hypertension, hyperlipidemia and a malignant follows.
	86	BRSTNOTO	The library was constructed using RNA isolated from diseased breast tissue removed from a 43-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated mildly proliferative fibrocystic changes with epithelial hyperplasia, papillomatosis, and duct ectasia. Pathology for the associated tumor tissue indicated invasive grade 4, nuclear grade 3 mammary adenocarcinoma with extensive comedo necrosis. Family history included epilepsy, cardiovascular disease, and type II diabetes.
81	66	BRAINOTO 9	The library was constructed using RNA isolated from brain tissue removed from a Caucasian male fetus who died at 23 weeks' gestation.
	100	THP1AZSO 8	The library was constructed using RNA isolated from 5.76 million clones from a 5-aza-2'-deoxycytidine treated THP-1 cell library. The library was subjected to subtractive hybridization using 5 million clones from an untreated THP-1 cell library. Hybridization conditions were adapted from Swaroop et al., NAR (1991) 19:1954; and Bonaldo et al., Genome Research (1996) 6:791. THP-1 (ATCC TIB 202) is a human promonocyte cell line derived from peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia.
	101	LUNGTUT1 2	The library was constructed using RNA isolated from tumorous lung tissue removed from a 70-year-old Caucasian female during a lung lobectomy of the left upper lobe. Pathology indicated grade 3 (of 4) adenocarcinoma and vascular invasion. Patient history included tobacco abuse, depressive disorder, anxiety state, and skin cancer. Family history included cerebrovascular disease, congestive heart failure, colon cancer, depressive disorder, and primary liver.
	102	HEAONOTO 5	The library was constructed using RNA isolated from aortic tissue removed from a 17- Year-old Hispanic female who died from a gunshot wound
	103	HEAONOTO 5	The library was constructed using RNA isolated from aortic tissue removed from a 17- year-old Hispanic female who died from a qunshot wound.

# TABLE 4 (conf

SEC ID NO:	Library	Library Comment
104	EPIGNOT0 1	The library was constructed using RNA isolated from epiglottic tissue removed from a 71-year-old male during laryngectomy with right parathyroid biopsy. Pathology for the associated tumor tissue indicated recurrent grade 1 papillary thyroid carcinoma.
105	CONCNOT0 1	issue re ion. Pat noma for eura. Pa al secre ic stoma y histor c corona cancer.
106	BRONNOT0 1	The library was constructed using RNA isolated from bronchial tissue removed from a 15-year-old Caucasian male.
107	BRONNOT0 1	10 1
108	LIVRNOT0 3	
. 109	LUNGNON0	The normalized library was constructed from 2.56 million independent clones from a lung tissue library. RNA was isolated from lung tissue removed from the left lobe a 58-year-old Caucasian male during a segmental lung resection. Pathology for the associated tumor tissue indicated a metastatic grade 3 (of 4) osteosarcoma. Patient history included soft tissue cancer, secondary cancer of the lung, prostate cancer, acute duodenal ulcer with hemorrhage, and radiation therapy to the retroperitoneum. Family history included prostate cancer, breast cancer, and acute leukemia. The normalization and hybridization conditions were adapted from Soares et al., PNAS (1994) 91:9228; Swaroop et al., NAR (1991) 19:1954; and Bonaldo et al., Genome
110	BRAIHCTO 2	The library was constructed using RNA isolated from diseased choroid plexus tissue removed from the brain of a 57-year-old Caucasian male who died from a cerebrovascular accident. Patient history included Huntington's disease and emphysema.

# Table.

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Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	ESTs: Probability value= 1.0E-8 o less Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater. fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88- 105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

# Table 5 (cont

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Normalized quality score SGCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186- 194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for pattems that matched those defined in Prosite.	Bairoch et al. <u>supra;</u> Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

WO 00/44900

PCT/US00/02237

### What is claimed is:

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- 1. An isolated polypeptide comprising:
- a) an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3-5, SEQ ID NO:7-14, SEQ ID NO:16-31, SEQ ID NO:33-34, SEQ ID NO:36-40, SEQ ID NO:42-48, SEQ ID NO:50-55.
  - b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3-5, SEQ ID NO:7-14, SEQ ID NO:16-31, SEQ ID NO:33-34, SEQ ID NO:36-40, SEQ ID NO:42-48, SEQ ID NO:50-55,
  - c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3-5, SEQ ID NO:7-14, SEQ ID NO:16-31, SEQ ID NO:33-34, SEQ ID NO:36-40, SEQ ID NO:42-48, SEQ ID NO:50-55, or
  - d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3-5, SEQ ID NO:7-14, SEQ ID NO:16-31, SEQ ID NO:33-34, SEQ ID NO:36-40, SEQ ID NO:42-48, SEQ ID NO:50-55.
- An isolated polypeptide of claim 1, having an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3-5, SEQ ID NO:7-14, SEQ ID NO:16-31, SEQ ID NO:33-34, SEQ ID NO:36-40,SEQ ID NO:42-48, SEQ ID NO:50-55.
  - 3. An isolated polynucleotide encoding a polypeptide of claim 1.
- 4. An isolated polynucleotide of claim 3, having a sequence selected from the group consisting of SEQ ID NO:56-110.
  - 5. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.
    - 6. A cell transformed with a recombinant polynucleotide of claim 5.
      - 7. A transgenic organism comprising a polynucleotide of claim 5.
      - 8. A method for producing a polypeptide of claim 1, the method comprising:
      - a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said

WO 00/44900 PCT/US00/02237

cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and

b) recovering the polypeptide so expressed.

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- 9. An isolated antibody which specifically binds to a polypeptide of claim 1.
- 10. An isolated polynucleotide comprising:
- a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:56-110,
- b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:56-110,
  - c) a polynucleotide sequence complementary to a), or
  - d) a polynucleotide sequence complementary to b).
- 11. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 10.
- 12. A method for detecting a target polynucleotide in a sample, said target polynucleotide
   20 having a sequence of a polynucleotide of claim 10, the method comprising:
  - a) hybridizing the sample with a probe comprising at least 16 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide, and
  - b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.
    - 13. A method of claim 12, wherein the probe comprises at least 30 contiguous nucleotides.
- 30 14. A method of claim 12, wherein the probe comprises at least 60 contiguous nucleotides.
  - 15. A pharmaceutical composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.
- 35 16. A method of treating a disease or condition associated with decreased expression of

WO 00/44900 PCT/US00/02237

functional NuABP, comprising administering to a patient in need of such treatment the pharmaceutical composition of claim 15.

- 17. A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:
  - a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
  - b) detecting agonist activity in the sample.
- 18. A pharmaceutical composition comprising an agonist compound identified by a method10 of claim 17 and a pharmaceutically acceptable excipient.
  - 19. A method of treating a disease or condition associated with decreased expression of functional NuABP, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 18.

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- 20. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:
  - a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
  - b) detecting antagonist activity in the sample.

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- 21. A pharmaceutical composition comprising an antagonist compound identified by a method of claim 20 and a pharmaceutically acceptable excipient.
- 22. A method for treating a disease or condition associated with overexpression of functional
   NuABP, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 21.
  - 23. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 4, the method comprising:
    - a) exposing a sample comprising the target polynucleotide to a compound, and
    - b) detecting altered expression of the target polynucleotide.





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(54) Title: NUCLEIC-ACID BINDING PROTEINS

(57) Abstract: The invention provides human nucleic-acid binding proteins (NuABP) and polynucleotides which identify and encode NuABP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of NuABP.



# DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

As a below named inventor, I hereby declare that:

the specification of which:

My residence, post office address and citizenship are as stated below next to my name, and

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

### **NUCLEIC-ACID BINDING PROTEINS**

// is attached hereto.	•
/_/ was filed on as application Serial contains an X //, was amended on	
/X / was filed as Patent Cooperation Treaty internation January 28, 2000, this box contains an X /_/, was amended Article 19 on 2001, and if this box contains an X /_	on under Patent Cooperation Treaty
I hereby state that I have reviewed and understand t specification, including the claims, as amended by any amen	
I acknowledge my duty to disclose information whice application in accordance with Title 37, Code of Federal Re	
I hereby claim the benefit under Title 35, United States foreign application(s) for patent or inventor's certificate ind Treaty international applications(s) designating at least one indicated below and have also identified below any foreign certificate and Patent Cooperation Treaty international application than the United States for the same subject matter and application for said subject matter the priority of which is c	licated below and of any Patent Cooperation country other than the United States application(s) for patent or inventor's lication(s) designating at least one country d having a filing date before that of the

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Country	Number	Filing Date	Priority Claimed
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			/_/ Yes /_/ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

Application		Status (Pending,
Serial No.	Filed	Abandoned, Patented)
60/117,905	January 29, 1999	Expired
60/117,904	January 29, 1999	Expired

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner required by the first paragraph of Title 35, United States Code §112, I acknowledge my duty to disclose material information as defined in Title 37 Code of Federal Regulations, §1.56(a) which occurred between the filing date(s) of the prior application(s) and the national or Patent Cooperation Treaty international filing date of this application:

Application		Status (Pending,	
Serial No.	Filed	Abandoned, Patented)	
I hereby appo	oint the following:		12

Lucy J. Billings	Reg. No. 36,749
Michael C. Cerrone	Reg. No. 39,132
Diana Hamlet-Cox	Reg. No. 33,302
Richard C. Ekstrom	Reg. No. 37,027
Barrie D. Greene	Reg. No. 46,740
Lynn E. Murry	Reg. No. 42,918
Shirley A. Recipon	Reg. No. 47,016
Susan K. Sather	Reg. No. 44,316
Michelle M. Stempien	Reg. No. 41,327
David G. Streeter	Reg. No. 43,168
Stephen Todd	Reg. No. 47,139
P. Ben Wang	Reg. No. 41,420

respectively and individually, as my patent attorneys and/or agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Please address all communications to:

# LEGAL DEPARTMENT INCYTE GENOMICS, INC. 3160 PORTER DRIVE, PALO ALTO, CA 94304

TEL: 650-855-0555 FAX: 650-849-8886 or 650-845-4166

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

	1-00	
First Joint Inventor:	Full name:	Y. Tom Tang
	Signature:	4. halos
	Date:	Spt. 10, 2001
	Citizenship	<b>United States of America</b>
	Residence:	San Jose, California CA
	P.O. Address:	4230 Ranwick Court
		San Jose, California 95118
	2-00	
<b>Second Joint Inventor:</b>	Full name:	Preeti Lal
	Signature:	Prechi W
	Date:	September 10, 2001
	Citizenship	India
	Residence:	Santa Clara, California 🔘 😝
	P.O. Address:	P.O. Box 5142 Santa Clara, California 95056

Valley, California 94552

	3-00	
Third Joint Inventor:	Full name:	Jennifer L. Hillman
	Signature:	- Juil / Ham
	Date:	System 2 (, 2001
	Citizenship	United States of America
	Residence:	Mountain View, California 🦳
	P.O. Address:	230 Monroe Drive, #17 Mountain View, California 94040
	4-00	
Fourth Joint Inventor:	Full name:	Henry Yue
routh Joint inventor.	Signature:	then he
	Date:	September 34 , 2001
	Citizenship	United States of America
	Residence:	Sunnyvale, California 📿
	P.O. Address:	826 Lois Avenue
		Sunnyvale, California 94087
	5-W	
Fifth Joint Inventor:	Full name:	Yalda Azimzai
	Signature:	Anda (hymzn)
	Date:	Usephorber 13, 2001
	Citizenship	United States of America
	Residence:	Castro Valley, California CA
	P.O. Address:	5518 Boulder Canyon Dr. Castro

	6-00	
Sixth Joint Inventor:	Full name:	Dyung Aina M. Lu
	Signature:	Siralu
	Date:	Sept 7 , 2001
	Citizenship	United States of America
	Residence:	San Jose, California
	P.O. Address:	233 Coy Drive
		San Jose, California 95123
	7-00	
<b>Seventh Joint Inventor:</b>	Full name:	Mariah R. Baughn
	Signature:	Mile R. Ble
	Date:	September 5, 2001
	Citizenship	United States of America
	Residence:	San Leandro, California
	P.O. Address:	14244 Santiago Road
		San Leandro, California 94577
	8-00	
<b>Eighth Joint Inventor:</b>	Full name:	Bao Tran
	Signature:	
	Date:	, 2001
	Citizenship	United States of America
	Residence:	Santa Clara, California
	P.O. Address:	750 Salberg Avenue
		Santa Clara, California95051

	9-50	
Ninth Joint Inventor:	Full name:	Leo L. Shih
	Signature:	
	Date:	, 2001
	Citizenship	<b>United States of America</b>
	Residence:	East Palo Alto, California
	P.O. Address:	908 O'Connor St. East Palo Alto, California 94303
Tenth Joint Inventor:	/ひ~の Full name:	) J <u>anice Au-Young</u>
	Signature:	Samue Che- George
	Date:	September 7, 2001
	Citizenship	United States of America
	Residence:	Brisbane, California CA
	P.O. Address:	233 Golden Eagle Lane Brisbane, California 94005

# DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

As a below named inventor, I hereby declare that:

the specification of which:

/ / is attached hereto.

74754

My residence, post office address and citizenship are as stated below next to my name, and

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

### NUCLEIC-ACID BINDING PROTEINS

// was filed on	as application Serial No	and if this box
	nded on	
/ X / was filed as Patent	Cooperation Treaty international application	on No. PCT/US00/02237 on
	ntains an X /_/, was amended on under Pa	
	and if this box contains an X /_/, was amer	
•	ave reviewed and understand the contents aims, as amended by any amendment refer	
•	ty to disclose information which is material h Title 37, Code of Federal Regulations, §	
I hereby claim the ber	nefit under Title 35, United States Code, §	119 or §365(a)-(b) of any
foreign application(s) for pate	ent or inventor's certificate indicated below	v and of any Patent Cooperation
Treaty international application	ons(s) designating at least one country oth	er than the United States
•	o identified below any foreign application(	
certificate and Patent Cooper	ration Treaty international application(s) de	esignating at least one country
-	for the same subject matter and having a fi	_
application for said subject m	atter the priority of which is claimed:	-

Country	Number	Filing Date	Priority Claimed
			/_/ Yes /_/ No
			/_/ Yes /_/ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

Application		Status (Pending,
Serial No.	Filed	Abandoned, Patented)
60/117,905	January 29, 1999	Expired
60/117,904	January 29, 1999	Expired

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner required by the first paragraph of Title 35, United States Code §112, I acknowledge my duty to disclose material information as defined in Title 37. Code of Federal Regulations, §1.56(a) which occurred between the filing date(s) of the prior application(s) and the national or Patent Cooperation Treaty international filing date of this application:

Application		Status (Pending,
Serial No.	Filed	Abandoned, Patented)

I hereby appoint the following:

Lucy J. Billings	Reg. No. 36,749
Michael C. Cerrone	Reg. No. 39,132
Diana Hamlet-Cox	Reg. No. 33,302
Richard C. Ekstrom	Reg. No. 37,027
Barrie D. Greene	Reg. No. 46,740
Lynn E. Murry	Reg. No. 42,918
Shirley A. Recipon	Reg. No. 47,016
Susan K. Sather	Reg. No. 44,316
Michelle M. Stempien	Reg. No. 41,327
David G. Streeter	Reg. No. 43,168

respectively and individually, as my patent attorneys and/or agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Please address all communications to:

### LEGAL DEPARTMENT INCYTE GENOMICS, INC. 3160 PORTER DRIVE, PALO ALTO, CA 94304

TEL: 650-855-0555 FAX: 650-849-8886 or 650-845-4166

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Y. Tom Tang

	Signature:	
	Date:	, 2001
	Citizenship	United States of America
	Residence:	San Jose, California
	P.O. Address:	4230 Ranwick Court San Jose, California 95118
Second Joint Inventor:	Full name:	Preeti Lal
•	Signature:	
	Date:	, 2001
	Citizenship	India
	Residence:	Santa Clara, California
	P.O. Address:	P.O. Box 5142 Santa Clara, California 95056

Full name:

**First Joint Inventor:** 

Third Joint Inventor:	Full name:	Jennifer L. Hillman
	Signature:	
	Date:	, 2001
	Citizenship	United States of America
	Residence:	Mountain View, California
	P.O. Address:	230 Monroe Drive, #17 Mountain View, California 94040
Fourth Joint Inventor:	Full name:	Henry Yue
rourth Joint Inventor.	Signature:	Hemy 1 de
	Date:	, 2001
	Citizenship	United States of America
	Residence:	Sunnyvale, California
	P.O. Address:	826 Lois Avenue Sunnyvale, California 94087
Fifth Joint Inventor:	Full name:	\$7-1-J- A
rum joint inventor:		Yalda Azimzai
	Signature: Date:	, 2001
	Citizenship	United States of America
	Residence:	Castro Valley, California
	P.O. Address:	5518 Boulder Canyon Dr. Castro Valley, California 94552

Santa Clara, California95051

Sixth Joint Inventor:	Full name:	Dyung Aina M. Lu
	Signature:	
	Date:	, 2001
	Citizenship	United States of America
	Residence:	San Jose, California
	P.O. Address:	233 Coy Drive San Jose, California 95123
	T. II	
Seventh Joint Inventor:	Full name:	Mariah R. Baughn
	Signature:	
	Date:	, 2001
	Citizenship	United States of America
	Residence:	San Leandro, California
	P.O. Address:	14244 Santiago Road San Leandro, California 94577
		1
<b>Eighth Joint Inventor:</b>	Full name:	Bao Tran
	Signature:	
	Date:	Set 26, 2001
	Citizenship	United States of America
	Residence:	Santa Clara, California
	P.O. Address:	750 Salberg Avenue

Ninth Joint Inventor:	Full name:	Leo L. Shih
	Signature:	
	Date:	, 2001
	Citizenship	United States of America
	Residence:	East Palo Alto, California
	P.O. Address:	908 O'Connor St. East Palo Alto, California 94303
Fenth Joint Inventor:	Full name:	Janice Au-Young
<b>V</b>	Signature:	June Mu-Toung
	Date:	, 2001
	Citizenship	United States of America
	Residence:	Brisbane, California
	P.O. Address:	233 Golden Eagle Lane Brisbane, California 94005

## DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

#### **NUCLEIC-ACID BINDING PROTEINS**

the specification of which:		
// is attached hereto.		
	as application Serial No	
January 28, 2000, this box co	Cooperation Treaty international application of the contains an X /_/, was amended on under Pand if this box contains an X /_/, was amen	atent Cooperation Treaty
•	ave reviewed and understand the contents aims, as amended by any amendment refer	

I acknowledge my duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim the benefit under Title 35, United States Code, §119 or §365(a)-(b) of any foreign application(s) for patent or inventor's certificate indicated below and of any Patent Cooperation Treaty international applications(s) designating at least one country other than the United States indicated below and have also identified below any foreign application(s) for patent or inventor's certificate and Patent Cooperation Treaty international application(s) designating at least one country other than the United States for the same subject matter and having a filing date before that of the application for said subject matter the priority of which is claimed:

1

Country	Number	Filing Date	Priority Claimed
			/_/ Yes /_/ No
			/ <u>/</u> Yes / <u>/</u> No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

Application		Status (Pending,
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Serial No.	Filed	Abandoned, Patented)

### I hereby appoint the following:

Lucy J. Billings	Reg. No. 36,749
Michael C. Cerrone	Reg. No. 39,132
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Richard C. Ekstrom	Reg. No. 37,027
Barrie D. Greene	Reg. No. 46,740
Lynn E. Murry	Reg. No. 42,918
Shirley A. Recipon	Reg. No. 47,016
Susan K. Sather	Reg. No. 44,316
Michelle M. Stempien	Reg. No. 41,327
David G. Streeter	Reg. No. 43,168
P. Ben Wang	Reg. No. 41,420

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FAX: 650-849-8886 or 650-845-4166

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First Joint Inventor:	Full name:	Y. Tom Tang	
	Signature:		
	Date:	, 2001	
	Citizenship	United States of America	
·	Residence:	San Jose, California	
	P.O. Address:	4230 Ranwick Court San Jose, California 95118	
Second Joint Inventor:	Full name:	Preeti Lal	
	Signature:		
	Date:	, 2001	
	Citizenship	India	
	Residence:	Santa Clara, California	
	P.O. Address:	P.O. Box 5142 Santa Clara, California 95056	

Third Joint Inventor:	Full name:	Jennifer L. Hillman	
	Signature:		
	Date:	, 2001	
	Citizenship	United States of America	
	Residence:	Mountain View, California	
	P.O. Address:	230 Monroe Drive, #17 Mountain View, California 94040	
Fourth Joint Inventor:	Full name:	Henry Yue	
	Signature:		
	Date:	, 2001	
•	Citizenship	<b>United States of America</b>	
·	Residence:	Sunnyvale, California	
	P.O. Address:	826 Lois Avenue Sunnyvale, California 94087	
Fifth Joint Inventor:	Full name:	Yalda Azimzai	
	Signature:		
	Date:	, 2001	
	Citizenship	United States of America	
	Residence:	Castro Valley, California	
	P.O. Address:	5518 Boulder Canyon Dr. Castro Valley, California 94552	

Sixth Joint Inventor:	Full name:	Dyung Aina M. Lu
	Signature:	
	Date:	, 2001
	Citizenship	United States of America
	Residence:	San Jose, California
	P.O. Address:	233 Coy Drive San Jose, California 95123
Seventh Joint Inventor:	Full name:	Mariah R. Baughn
•	Signature:	
	Date:	, 2001
·	Citizenship	United States of America
,	Residence:	San Leandro, California
	P.O. Address:	14244 Santiago Road San Leandro, California 94577
Eighth Joint Inventor:	Full name:	Bao Tran
	Signature:	
	Date:	, 2001
	Citizenship	<b>United States of America</b>
	Residence:	Santa Clara, California
	P.O. Address:	750 Salberg Avenue Santa Clara, California95051

**Ninth Joint Inventor:** 

Full name:

Leo L. Shih

Signature:

· ·

Date:

october 27

, 2001

Citizenship

**United States of America** 

Residence:

East Palo Alto, California

P.O. Address:

908 O'Connor St.

East Palo Alto, California 94303

**Tenth Joint Inventor:** 

Full name:

Janice Au-Young

Signature:

Date:

, 2001

Citizenship

**United States of America** 

Residence:

Brisbane, California

P.O. Address:

233 Golden Eagle Lane

Brisbane, California 94005

## SEQUENCE LISTING

```
<110> INCYTE PHARMACEUTICALS, INC.
       TANG, Y. Tom
      LAL, Preeti
      HILLMAN, Jennifer L.
      YUE, Henry
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      LU, Aina M.D.
      BAUGHN, Mariah R.
      TRAN, Bao
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      AU-YOUNG, Janice
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医抗原素 建铁矿 医毛毛 医原

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val	GIU	VIG	TTP	605	пåр	пеп	1111	AT 9	610	Jau	JLY		-10	615

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Lys Thr Asn Val Gln Gln Cys Tyr Cys Tyr Cys Gly Gly Pro Gly

Asp Trp Tyr Leu Lys Met Leu Gln Cys Cys Lys Cys Lys Gln Trp

WO 00/44900

PCT/US00/02237

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Lys	Arg	Thr	Arg		Gly	Arg	Ser	Trp		Ala	Ala	Ile	Pro	
Leu	Arg	Arg	Arg	Arg	Gly	Arg	Leu	Pro	Arg	Arg	Ala	Leu	Gln	Thr
Gln	Asn	Ser	Glu		Val	Lys	Asp	Asp		Gly	Lys	Glu	Asp	_
Gln	Phe	Asp	Glu		Asn	Thr	Glu	Ile		Asn	Asn	Leu	Ala	
Gln	Glu	Leu	Gln		Asn	His	Leu	Lys		Ser	Ile	Thr	Ser	_
Phe	Gly	Ala	Ala		Arg	Ile	Ala	Cys		Glu	Lys	Tyr	Arg	
Leu	Ala	Arg	Arg		Thr	Leu	Asp	Gly	_	Val	Gln	Туг	Leu	
Glu	Trp	Glu	Gly	575 Ala 590	Thr	Ala	Ser		580					585

<210> 3

<211> 534

<212> PRT

<213> Homo sapiens

<220>

<223> Incyte ID No.: 116208CD1 <400> 3 Met Arg Ala Leu His Leu Leu Lys Ser Gly Cys Ser Pro Ala Val Gln Ile Lys Ile Arg Glu Leu Tyr Arg Arg Arg Tyr Pro Arg Thr Leu Glu Gly Leu Ser Asp Leu Ser Thr Ile Lys Ser Ser Val Phe Ser Leu Asp Gly Gly Ser Ser Pro Val Glu Pro Asp Leu Ala Val Ala Gly Ile His Ser Leu Pro Ser Thr Ser Val Thr Pro His Ser Pro Ser Ser Pro Val Gly Ser Val Leu Leu Gln Asp Thr Lys Pro Thr Phe Glu Met Gln Gln Pro Ser Pro Pro Ile Pro Pro Val His Pro Asp Val Gln Leu Lys Asn Leu Pro Phe Tyr Asp Val Leu Asp Val Leu Ile Lys Pro Thr Ser Leu Val Gln Ser Ser Ile Gln Arg Phe Gln Glu Lys Phe Phe Ile Phe Ala Leu Thr Pro Gln Gln Val Arg Glu Ile Cys Ile Ser Arg Asp Phe Leu Pro Gly Gly Arg Arg Asp Tyr Thr Val Gln Val Gln Leu Arg Leu Cys Leu Ala Glu Thr Ser Cys Pro Gln Glu Asp Asn Tyr Pro Asn Ser Leu Cys Ile Lys Val Asn Gly Lys Leu Phe Pro Leu Pro Gly Tyr Ala Pro Pro Pro Lys Asn Gly Ile Glu Gln Lys Arg Pro Gly Arg Pro Leu Asn Ile Thr Ser Leu Val Arg Leu Ser Ser Ala Val Pro Asn Gln Ile Ser Ile Ser Trp Ala Ser Glu Ile Gly Lys Asn Tyr Ser Met Ser Val Tyr Leu Val Arg Gln Leu Thr Ser Ala Met Leu Leu Gln Arg Leu Lys Met Lys Gly Ile Arg Asn Pro Asp His Ser Arg Ala Leu Ser Lys Glu Lys Leu Thr Ala Asp Pro Asp Ser Glu Ile Ala Thr Thr Ser Leu Arg Val Ser Leu Met Cys Pro Leu Gly Lys Met Arg Leu Thr Ile Pro Cys Arg Ala Val Thr Cys Thr His Leu Gln Cys Phe Asp Ala Ala Leu Tyr Leu Gln Met Asn Glu Lys Lys Pro Thr Trp Ile Cys Pro Val Cys Asp Lys Lys Ala Ala Tyr Glu Ser Leu Ile Leu Asp Gly Leu Phe Met Glu Ile Leu Asn Asp Cys Ser Asp Val Asp Glu Ile Lys Phe Gln Glu Asp Gly Ser Trp Cys Pro Met Arg Pro Lys Lys Glu Ala Met Lys Val Ser Ser Gln Pro Cys Thr Lys Ile Glu Ser Ser Ser Val Leu Ser Lys Pro Cys Ser Val Thr Val Ala Ser Glu Ala Ser Lys Lys Val Asp Val Ile Asp Leu Thr 

<221> misc-feature

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Ile Glu Ser Ser Ser Asp Glu Glu Glu Asp Pro Pro Ala Lys Arg
                440
                                                          450
                                     445
Lys Cys Ile Phe Met Ser Glu Thr Gln Ser Ser Pro Thr Lys Gly
                455
                                                          465
                                     460
Val Leu Met Tyr Gln Pro Ser Ser Val Arg Val Pro Ser Val Thr
                470
                                     475
Ser Val Asp Pro Ala Ala Ile Pro Pro Ser Leu Thr Asp Tyr Ser
                485
                                     490
                                                          495
Val Pro Phe His His Thr Pro Ile Ser Ser Met Ser Ser Asp Leu
                500
                                     505
Pro Gly Glu Gln Arg Arg Asn Asp Ile Asn Asn Glu Leu Lys Leu
                515
                                    520
Gly Thr Ser Ser Asp Thr Val Gln Gln
                530
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<211> 255
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<220>
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Met Lys Ile Ile Ser Glu Asn Val Pro Ser Tyr Lys Thr His Glu
 1
                                                           15
                                      10
Ser Leu Thr Leu Pro Arg Arg Thr His Asp Ser Glu Lys Pro Tyr
                 20
                                      25
Glu Tyr Lys Glu Tyr Glu Lys Val Phe Ser Cys Asp Leu Glu Phe
                 35
                                      40
                                                           45
Asp Glu Tyr Gln Lys Ile His Thr Gly Gly Lys Asn Tyr Glu Cys
                 50
                                      55
                                                           60
Asn Gln Cys Trp Lys Thr Phe Gly Ile Asp Asn Ser Ser Met Leu
                                                           75
                                      70
                 65
Gln Leu Asn Ile His Thr Gly Val Lys Pro Cys Lys Tyr Met Glu
                 80
                                      85
                                                           90
Tyr Gly Asn Thr Cys Ser Phe Tyr Lys Asp Phe Asn Val Tyr Gln
                 95
                                     100
Lys Ile His Asn Glu Lys Phe Tyr Lys Cys Lys Glu Tyr Arg Arg
                110
                                    115
                                                          120
Thr Phe Glu Arg Val Gly Lys Val Thr Pro Leu Gln Arg Val His
                125
                                    130
                                                          135
Asp Gly Glu Lys His Phe Glu Cys Ser Phe Cys Gly Lys Ser Phe
                140
                                     145
                                                          150
Arg Val His Ala Gln Leu Thr Arg His Gln Lys Ile His Thr Asp
                155
                                    160
Glu Lys Thr Tyr Lys Cys Met Glu Cys Gly Lys Asp Phe Arg Phe
                170
                                    175
                                                          180
His Ser Gln Leu Thr Glu His Gln Arg Ile His Thr Gly Glu Lys
                185
                                    190
                                                          195
Pro Tyr Lys Cys Met His Cys Glu Lys Val Phe Arg Ile Ser Ser
                200
                                    205
                                                          210
Gln Leu Ile Glu His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr
                215
                                    220
                                                         225
Ala Cys Lys Glu Cys Gly Lys Ala Phe Gly Val Cys Arg Glu Leu
                230
                                    235
Ala Arg His Gln Arg Ile His Thr Gly Lys Tyr Cys Gly Trp Ile
                245
                                    250
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高温光线的 医胸囊肠囊膜 网络绿

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<210> 5
<211> 562
<212> PRT
<213> Homo sapiens
<220>
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Met Ala Ser Val Ser Ala Leu Thr Glu Glu Leu Asp Ser Ile Thr
                                       10
Ser Glu Leu His Ala Val Glu Ile Gln Ile Gln Glu Leu Thr Glu
                  20
                                       25
                                                           3.0
Arg Gln Glu Leu Ile Gln Lys Lys Val Leu Thr Lys Lys
                  35
                                       40
                                                            45
Ile Lys Gln Cys Leu Glu Asp Ser Asp Ala Gly Ala Ser Asn Glu
                  50
                                       55
Tyr Asp Ser Ser Pro Ala Ala Trp Asn Lys Glu Asp Phe Pro
                                                          Trp
                  65
                                       70
Ser Gly Lys Val Lys
                    Asp Ile Leu Gln Asn Val Phe Lys Leu Glu
                                                           90
                  80
                                       85
Lys Phe Arg Pro Leu Gln Leu Glu Thr Ile Asn Val Thr Met Ala
                  95
                                      100
                                                          105
Gly Lys Glu Val Phe Leu Val Met Pro Thr Gly Gly Gly Lys Ser
                110
                                      115
Leu Cys Tyr Gln Leu Pro Ala Leu Cys Ser Asp Gly Phe Thr Leu
                                     130
                125
                                                          135
Val Ile Cys Pro Leu Ile Ser Leu Met Glu Asp Gln Leu Met Val
                140
                                     145
                                                          150
Leu Lys Gln Leu Gly Ile Ser Ala Thr Met Leu Asn Ala Ser Ser
                155
                                     160
                                                          165
Ser Lys Glu His Val Lys Trp Val His Ala Glu Met Val Asn Lys
                170
                                      175
Asn Ser Glu Leu Lys Leu Ile Tyr Val Thr Pro Glu Lys Ile Ala
                185
                                     190
Lys Ser Lys Met Phe Met Ser Arg Leu Glu Lys Ala Tyr Glu Ala
                200
                                     205
                                                          210
Arg Arg Phe Thr Arg Ile Ala Val Asp Glu Val His Cys Cys Ser
                215
                                     220
                                                          225
Gln Trp Gly His Asp Phe Arg Pro Asp Tyr Lys Ala Leu Gly Ile
                230
                                     235
                                                          240
Leu Lys Arg Gln Phe Pro Asn Ala Ser Leu Ile Gly Leu Thr Ala
                                                          255
                245
                                     250
Thr Ala Thr Asn His Val Leu Thr Asp Ala Gln Lys Ile Leu Cys
                260
                                     265
                                                          270
Ile Glu Lys Cys Phe Thr Phe Thr Ala Ser Phe Asn Lys Pro Asp
                275
                                     280
Val Arg Phe Val Ile His His Ser Met Ser Lys Ser Met Glu Asn
                290
                                     295
                                                          300
Tyr Tyr Gln Glu Ser Gly Arg Ala Gly Arg Asp Asp Met Lys Ala
                305
                                     310
                                                          315
Asp Cys Ile Leu Tyr Tyr Gly Phe Gly Asp Ile Phe Arg Ile Ser
                320
                                     325
Ser Met Val Val Met Glu Asn Val Gly Gln Gln Lys Leu Tyr Glu
                335
                                     340
                                                          345
Met Val Ser Tyr Cys Gln Asn Ile Ser Lys Cys Arg Arg Val Leu
                350
                                     355
                                                          360
Met Ala Gln His Phe Asp Glu Val Trp Asn Ser Glu Ala Cys Asn
```

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370
                                                          375
Lys Met Cys Asp Asn Cys Cys Lys Asp Ser Ala Phe Glu Arg Lys
                380
                                     385
                                                          390
Asn Ile Thr Glu Tyr Cys Arg Asp Leu Ile Lys Ile Leu Lys Gln
                395
                                     400
Ala Glu Glu Leu Asn Glu Lys Leu Thr Pro Leu Lys Leu Ile Asp
                410
                                     415
Ser Trp Met Gly Lys Gly Ala Ala Lys Leu Arg Val Ala Gly Val
                425
                                     430
                                                          435
Val Ala Pro Thr Leu Pro Arg Glu Asp Leu Glu Lys Ile Ile Ala
                440
                                     445
                                                          450
His Phe Leu Ile Gln Gln Tyr Leu Lys Glu Asp Tyr Ser Phe Thr
                                     460
                                                          465
                455
Ala Tyr Ala Thr Ile Ser Tyr Leu Lys Ile Gly Pro Lys Ala Asn
                470
                                     475
Leu Leu Asn Asn Glu Ala His Ala Ile Thr Met Gln Val Thr Lys
                485
                                    490
Ser Thr Gln Asn Ser Phe Arg Ala Glu Ser Ser Gln Thr Cys His
                500
                                    505
                                                         510
Ser Glu Gln Gly Asp Lys Lys Ile Gly Gly Lys Lys Phe Gln Ala
                515
                                    520
Thr Ser Arg Arg Leu Gln Thr Cys Phe Ser Asn Leu Val Leu
                                    535
                530
Arg Ile Gln Glu Leu Arg Lys Glu Lys Ser Met Met Pro Asp Met
                                    550
                545
Thr Val Thr Lys Phe Ser Asn
                560
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<210> 6
<211> 432
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 320087CD1
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Met Ser Glu Leu Lys Asp Cys Pro Leu Gln Phe His Asp Phe Lys
                                                           15
                                      10
Ser Val Asp His Leu Lys Val Cys Pro Arg Tyr Thr Ala Val Leu
                                      25
Ala Arg Ser Glu Asp Asp Gly Ile Gly Ile Glu Glu Leu Asp Thr
                 35
Leu Gln Leu Glu Leu Glu Thr Leu Leu Ser Ser Ala Ser Arg Arg
                                      55
                                                           60
                 50
Leu Arg Val Leu Glu Ala Glu Thr Gln Ile Leu Thr Asp Trp Gln
                 65
                                     70
                                                           75
Asp Lys Lys Gly Asp Arg Arg Phe Leu Lys Leu Gly Arg Asp His
                                     85
                                                           90
                 80
Glu Leu Gly Ala Pro Pro Lys His Gly Lys Pro Lys Lys Gln Lys
                                    100
                                                          105
                 95
Leu Glu Gly Lys Ala Gly His Gly Pro Gly Pro Gly Pro Gly Arg
                                    115
                                                          120
                110
Pro Lys Ser Lys Asn Leu Gln Pro Lys Ile Gln Glu Tyr Glu Phe
                                    130
                125
Thr Asp Asp Pro Ile Asp Val Pro Arg Ile Pro Lys Asn Asp Ala
                                                         150
                140
                                    145
```

```
Pro Asn Arg Phe Trp Ala Ser Val Glu Pro Tyr Cys Ala Asp Ile
                                                          165
                155
                                     160
Thr Ser Glu Glu Val Arg Thr Leu Glu Glu Leu Leu Lys Pro Pro
                                                          180
                170
Glu Asp Glu Ala Glu His Tyr Lys Ile Pro Pro Leu Gly Lys His
                                     190
                185
   Ser Gln Arg Trp Ala Gln Glu Asp Leu Leu Glu Glu Gln Lys
                                     205
                                                          210
                200
Asp Gly Ala Arg Ala Ala Ala Val Ala Asp Lys Lys Gly Leu
                215
                                     220
                                                          225
Met Gly Pro Leu Thr Glu Leu Asp Thr Lys Asp Val Asp Ala Leu
                230
                                     235
                                                          240
Leu Lys Lys Ser Glu Ala Gln His Glu Gln Pro Glu Asp Gly Cys
                                                          255
                245
                                     250
Pro Phe Gly Ala Leu Thr Gln Arg Leu Leu Gln Ala Leu Val Glu
                                     265
                                                          270
                260
Glu Asn Ile Ile Ser Pro Met Glu Asp Ser Pro Ile Pro Asp Met
                                     280
                                                          285
                275
Ser Gly Lys Glu Ser Gly Ala Asp Gly Ala Ser Thr Ser Pro Arg
                                     295
                                                          300
                290
Asn Gln Asn Lys Pro Phe Ser Val Pro His Thr Lys Ser Leu Glu
                                     310
                                                          315
                305
Ser Arg Ile Lys Glu Glu Leu Ile Ala Gln Gly Leu Leu Glu Ser
                320
                                     325
                                                          330
Glu Asp Arg Pro Ala Glu Asp Ser Glu Asp Glu Val Leu Ala Glu
                335
                                     340
Leu Arg Lys Arg Gln Ala Glu Leu Lys Ala Leu Ser Ala His Asn
                350
                                     355
Arg Thr Lys Lys His Asp Leu Leu Arg Leu Ala Lys Glu Glu Val
                                     370
                                                         375
                365
Ser Arg Gln Glu Leu Arg Gln Arg Val Arg Met Ala Asp Asn Glu
                380
                                     385
                                                         390
Val Met Asp Ala Phe Arg Lys Ile Met Ala Ala Arg Gln Lys Lys
                                     400
                                                         405
                395
Arg Thr Pro Thr Lys Lys Glu Lys Asp Gln Ala Trp Lys Thr Leu
                                     415
                410
Lys Glu Arg Glu Ser Ile Leu Lys Leu Leu Asp Gly
                                     430
                425
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<210> 7
<211> 799
<212> PRT
<213> Homo sapiens
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<220>
<221> misc-feature
<223> 491271CD1

<400> 7 Met Pro Ser Gln Asn Tyr Asp Leu Pro Gln Lys Lys Gln Glu Lys Met Thr Lys Phe Gln Glu Ala Val Thr Phe Lys Asp Val Ala Val Val Phe Ser Arg Glu Glu Leu Arg Leu Leu Asp Leu Thr Gln Arg Lys Leu Tyr Arg Asp Val Met Val Glu Asn Phe Lys Asn Leu Val Ala Val Gly His Leu Pro Phe Gln Pro Asp Met Val Ser Gln Leu 

Gl	u Ala	Glu	Glu	Lys 80	Leu	Trp	Met	Met	Glu 85		Glu	Thr	Gln	Arg
Sę	r Ser	Lys	His	Gln 95	Asn	Lys	Met	Glu	Thr		Glr	Lys	Phe	Ala 105
Le	u Lys	Tyr	Leu	Ser 110	Asn	Gln	Glu	Leu	Ser 115		Trp	Glr	ılle	120
	s Gln			125					130					135
	r Gln			140					145					150
As	n Asn	Ile	Met	Asn 155	Pro	Lys	Gly	Asp	Ser 160		Ile	Tyr	Ile	Glu 165
As:	n Gln	Glu	Phe	Pro 170	Phe	Trp	Arg	Thr	Gln 175		Ser	Cys	Gly	Asn 180
Th	r Tyr	Leu	Ser	Glu 185	Ser	Gln	Ile	Gln	Ser 190		Gly	Lys	Gln	Ile 195
	p Val			200					205					210
	r Pro			215					220					225
	s Lys			230					235					240
	n Lys			245					250					255
	y Arg			260					265					270
	l His			275					280					285
	r His			290					295					300
Gl	ı Ser	Gly	Asp	Cys 305	Phe	Asn	Lys	Ser	Ser 310	Phe	His	Ser	Tyr	Gln 315
Se	r Asn	His	Thr	Gly 320	Glu	Lys	Ser	Tyr	Arg 325	Cys	Asp	Ser	Cys	Gly 330
Ly	s Gly	Phe	Ser	Ser 335	Ser	Thr	Gly	Leu	Ile 340	Ile	His	Tyr	Arg	Thr 345
	s Thr	_		350					355					360
Ph	e Ser	Gln	Ser	Ser 365	Asn	Phe	Gln	Суѕ	His 370	Gln	Arg	Val	His	Thr 375
Gl	ı Glu	Lys	Pro	Tyr 380	Lys	Cys	Glu	Glu	Cys 385	Gly	Lys	Gly	Phe	Gly 390
Tr	o Ser	Val	Asn	Leu 395	Arg	Val	His	Gln	Arg 400	Val	His	Arg	Gly	Glu 405
Ly	s Pro	Tyr	Lys	Cys 410	Glu	Glu	Суѕ	Gly	Lys 415	Gly	Phe	Thr	Gln	Ala 420
Ala	a His	Phe	His	Ile 425	His	Gln	Arg	Val	His 430	Thr	Gly	Glu	Lys	Pro 435
Ту	r Lys	Суѕ	Asp	Val 440	Cys	Gly	Lys	Gly	Phe 445	Ser	His	Asn	Ser	Pro 450
Let	ı Ile	Cys	His	Arg 455	Arg	Val	His	Thr	Gly 460	Glu	Lys	Pro	Tyr	Lys 465
Cy:	s Glu	Ala	Cys	Gly 470	Lys	Gly	Phe	Thr	Arg 475	Asn	Thr	Asp	Leu	His 480
Ile	∋ His	Phe	Arg		His	Thr	Gly	Glu		Pro	Tyr	Lys	Cys	
Glı	ı Cys	Gly	Lys		Phe	Ser	Gln	Ala		Asn	Leu	Gln	Val	
Gli	n Asn	Val	His		Gly	Glu	Lys	Arg	-	Lys	Суѕ	Glu	Thr	
Gl	y Lys	Gly	Phe		Gln	Ser	Ser	Lys		Gln	Thr	His	Gln	

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530
                                      535
                                                           540
Val His Thr Gly Glu Lys Pro Tyr Arg Cys Asp Val Cys Gly Lys
                545
                                     550
Asp Phe Ser Tyr Ser Ser Asn Leu Lys Leu His Gln Val Ile His
                560
                                     565
                                                           570
Thr Gly Glu Lys Pro Tyr Lys Cys Glu Glu Cys Gly Lys Gly Phe
                575
                                     580
Ser Trp Arg Ser Asn Leu His Ala His Gln Arg Val His Ser Gly
                590
                                     595
                                                           600
Glu Lys Pro Tyr Lys Cys Glu Gln Cys Asp Lys Ser Phe Ser Gln
                605
                                     610
                                                           615
Ala Ile Asp Phe Arg Val His Gln Arg Val His Thr Gly Glu Lys
                620
                                     625
                                                           630
Pro Tyr Lys Cys Gly Val Cys Gly Lys Gly Phe Ser Gln Ser Ser
                635
                                     640
                                                          645
Gly Leu Gln Ser His Gln Arg Val His Thr Gly Glu Lys Pro Tyr
                650
                                     655
                                                          660
Lys Cys Asp Val Cys Gly Lys Gly Phe Arg Tyr Ser Ser Gln Phe
                665
                                     670
                                                          675
Ile Tyr His Gln Arg Gly His Thr Gly Glu Lys Pro Tyr Lys Cys
                680
                                     685
                                                          690
Glu Glu Cys Gly Lys Gly Phe Gly Arg Ser Leu Asn Leu Arg His
                695
                                     700
His Gln Arg Val His Thr Gly Glu Lys Pro His Ile Cys Glu Glu
                710
                                     715
                                                          720
Cys Gly Lys Ala Phe Ser Leu Pro Ser Asn Leu Arg Val His Leu
                725
                                     730
                                                          735
Gly Val His Thr Arg Glu Lys Leu Phe Lys Cys Glu Glu Cys Gly
                740
                                     745
                                                          750
Lys Gly Phe Ser Gln Ser Ala Arg Leu Glu Ala His Gln Arg Val
                755
                                     760
                                                          765
His Thr Gly Glu Lys Pro Tyr Lys Cys Asp Ile Cys Asp Lys
                                                         Asp
                770
                                     775
Phe Arg His Arg Ser Arg Leu Thr Tyr His Gln Lys Val His Thr
                                     790
Gly Lys Lys Leu
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<210> 8
<211> 137
<212> PRT
<213> Homo sapiens
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<221> misc-feature
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<400> 8
Met Leu Ser Gly Arg Leu Val Leu Gly Leu Val Ser Met Ala Gly
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                                                           15
Arg Val Cys Leu Cys Gln Gly Ser Ala Gly Ser Gly Ala Ile Gly
                 20
                                      25
Pro Val Glu Ala Ala Ile Arg Thr Lys Leu Glu Glu Ala Leu Ser
                 35
                                      40
Pro Glu Val Leu Glu Leu Arg Asn Glu Ser Gly Gly His Ala Val
Pro Pro Gly Ser Glu Thr His Phe Arg Val Ala Val Val Ser Ser
                 65
                                     70
Arg Phe Glu Gly Leu Ser Pro Leu Gln Arg His Arg Leu Val His
```

85

100

Ala Ala Leu Ala Glu Glu Leu Gly Gly Pro Val His Ala Leu Ala

Ile Gln Ala Arg Thr Pro Ala Gln Trp Arg Glu Asn Ser Gln Leu

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110
                                      115
                                                          120
Asp Thr Ser Pro Pro Cys Leu Gly Gly Asn Lys Lys Thr Leu Gly
Thr Pro
<210> 9
<211> 230
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 615200CD1
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Met Val Gly Ala Gly Ile Ser Thr Pro Ser Gly Ile Pro Asp Phe
                                      10
Arg Ser Pro Gly Ser Gly Leu Tyr Ser Asn Leu Gln Gln Tyr Asp
                                      25
Leu Pro Tyr Pro Glu Ala Ile Phe Glu Leu Pro Phe Phe His
                                      40
                  35
Asn Pro Lys Pro Phe Phe Thr Leu Ala Lys Glu Leu Tyr Pro Gly
                 50
                                      55
Asn Tyr Lys Pro Asn Ile Thr His Tyr Phe Leu Arg Leu Leu His
                  65
                                      70
                                                          75
Asp Lys Gly Leu Leu Leu Arg Leu Tyr Thr Gln Asn Ile Asp Gly
                 80
                                      85
Leu Glu Arg Val Ser Gly Ile Pro Ala Ser Lys Leu Val Glu Ala
                 95
                                     100
                                                         105
His Gly Thr Phe Ala Ser Ala Thr Cys Thr Val Cys Gln Arg Pro
                110
                                     115
                                                         120
Phe Pro Gly Glu Asp Ile Arg Ala Asp Val Met Ala Asp Arg Val
                125
                                     130
Pro Arg Cys Pro Val Cys Thr Gly Val Val Lys Pro Asp Ile Val
                                     145
                140
                                                         150
Phe Phe Gly Glu Pro Leu Pro Gln Arg Phe Leu Leu His Val Val
                155
                                     160
                                                         165
Asp Phe Pro Met Ala Asp Leu Leu Leu Ile Leu Gly Thr Ser Leu
                170
                                     175
                                                         180
Glu Val Glu Pro Phe Ala Ser Leu Thr Glu Ala Val Arg Thr Gln
                185
                                     190
                                                         195
Phe Pro Asp Cys Ser Ser Thr Gly Thr Trp Trp Gly Pro Trp Leu
                200
                                     205
Gly Ile Leu Ala Ala Gly Thr Trp Pro Ser Trp Gly Thr Trp Phe
                                     220
                215
Thr Ala Trp Lys Ala
                230
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80

<sup>&</sup>lt;210> 10 <211> 446 <212> PRT <213> Homo sapiens

<221> misc-feature <223> Incyte ID No.: 997067CD1 <400> 10 Met Glu Thr Gln Ala Asp Leu Val Ser Gln Glu Pro Gln Ala Leu Leu Asp Ser Ala Leu Pro Ser Lys Val Pro Ala Phe Ser Asp Lys Asp Ser Leu Gly Asp Glu Met Leu Ala Ala Ala Leu Leu Lys Ala Lys Ser Gln Glu Leu Val Thr Phe Glu Asp Val Ala Val Tyr Phe Ile Arg Lys Glu Trp Lys Arg Leu Glu Pro Ala Gln Arg Asp Leu Tyr Arg Asp Val Met Leu Glu Asn Tyr Gly Asn Val Phe Ser Leu Asp Arg Glu Thr Arg Thr Glu Asn Asp Gln Glu Ile Ser Glu Asp Thr Arg Ser His Gly Val Leu Leu Gly Arg Phe Gln Lys Asp Ile Phe Lys Glu Ala Tyr Glu Arg Glu Val Ser Ser Gln Gly Leu Lys Leu Lys Arg Pro Leu Gly Asn Ser Pro Gly Glu Arg Leu Asn Arg Lys Met Pro Asp Phe Gly Gln Val Thr Val Glu Glu Lys Leu Thr Pro Arg Gly Glu Arg Ser Glu Lys Tyr Asn Asp Phe Gly Asn Ser Phe Thr Val Asn Ser Asn Leu Ile Ser His Gln Arg Leu Pro Val Gly Asp Arg Pro His Lys Cys Asp Glu Cys Ser Lys Ser Phe Asn Arg Thr Ser Asp Leu Ile Gln His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Asn Glu Cys Gly Lys Ala Phe Ser Gln Ser Ser His Leu Ile Gln His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Ser Asp Cys Gly Lys Thr Phe Ser Cys Ser Ser Ala Leu Ile Leu His Arg Arg Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Asn Glu Cys Gly Lys Thr Phe Ser Trp Ser Ser Thr Leu Thr His His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Ala Cys Asn Glu Cys Gly Lys Ala Phe Ser Arg Ser Ser Thr Leu Ile His His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Asn Glu Cys Gly Lys Ala Phe Ser Gln Ser Ser His Leu Tyr Gln His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Met Glu Cys Gly Gly Lys Phe Thr Tyr Ser Ser Gly Leu Ile Gln His Gln Arg Ile His Thr Gly Glu Asn Pro Tyr Glu Cys Ser Glu Cys Gly Lys Ala Phe Arg Tyr Ser Ser Ala Leu Val Arg His Gln Arg Ile His Thr Gly Glu Lys Pro Leu Asn Gly Ile Gly Met Ser Lys Ser Ser Leu Arg

<220>

Val Thr Thr Glu Leu Asn Ile Arg Glu Ser Thr

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<210> 11
<211> 428
<212> PRT
<213> Homo sapiens
<221> misc-feature
<223> Incyte ID NO.: 1443262CD1
<400> 11
Met Glu Pro Leu Lys Val Glu Lys Phe Ala Thr Ala Asn Arg Gly
                                      10
Asn Gly Leu Arg Ala Val Thr Pro Leu Arg Pro Gly Glu Leu Leu
                  20
                                      25
Phe Arg Ser Asp Pro Leu Ala Tyr Thr Val
                                         Cys Lys Gly Ser Arg
                                                           45
                                      40
                  35
                                         Lys Glu Lys Leu Met
Gly Val Val Cys Asp Arg Cys Leu Leu Gly
                                                           60
                                      55
                  50
                                         Cys Ser Ala Lys Cys
Arg Cys Ser Gln Cys Arg Val Ala Lys Tyr
                                                           75
                                      70
                  65
Gln Lys Lys Ala Trp Pro Asp His Lys Arg Glu Cys Lys Cys Leu
                                                           90
                                      85
                  80
Lys Ser Cys Lys Pro Arg Tyr Pro Pro Asp Ser Val Arg Leu Leu
                                     100
                  95
Gly Arg Val Val Phe Lys Leu Met Asp Gly Ala Pro Ser Glu Ser
                                                          120
                                     115
                 110
Glu Lys Leu Tyr Ser Phe Tyr Asp Leu Glu Ser Asn Ile Asn Lys
                                     130
                                                          135
                 125
Leu Thr Glu Asp Lys Lys Glu Gly Leu Arg Gln Leu Val Met Thr
                                     145
                 140
Phe Gln His Phe Met Arg Glu Glu Ile Gln Asp Ala Ser Gln Leu
                                                          165
                                     160
                 155
Pro Pro Ala Phe Asp Leu Phe Glu Ala Phe Ala Lys Val Ile Cys
                                                          180
                                     175
                 170
Asn Ser Phe Thr Ile Cys Asn Ala Glu Met Gln Glu Val Gly Val
                                                          195
                                     190
                 185
Gly Leu Tyr Pro Ser Ile Ser Leu Leu Asn His Ser Cys Asp Pro
                 200
                                     205
Asn Cys Ser Ile Val Phe Asn Gly Pro His Leu Leu Leu Arg Ala
                                     220
                 215
Val Arg Asp Ile Glu Val Gly Glu Glu Leu Thr Ile Cys Tyr Leu
                                     235
                 230
Asp Met Leu Met Thr Ser Glu Glu Arg Arg Lys Gln Leu Arg Asp
                                     250
                                                          255
                 245
Gln Tyr Cys Phe Glu Cys Asp Cys Phe Arg Cys Gln Thr Gln Asp
                                                          270
                                     265
                 260
Lys Asp Ala Asp Met Leu Thr Gly Asp Glu Gln Val Trp Lys Glu
                                     280
                                                          285
                 275
Val Gln Glu Ser Leu Lys Lys Ile Glu Glu Leu Lys Ala His Trp
                                                          300
                 290
                                     295
Lys Trp Glu Gln Val Leu Ala Met Cys Gln Ala Ile Ile Ser Ser
                                                          315
                                     310
                 305
Asn Ser Glu Arg Leu Pro Asp Ile Asn Ile Tyr Gln Leu Lys Val
                 320
```

```
Leu Asp Cys Ala Met Asp Ala Cys Ile Asn Leu Gly Leu Leu Glu
                335
                                     340
Glu Ala Leu Phe Tyr Gly Thr Arg Thr Met Glu Pro Tyr Arg Ile
                350
                                     355
                                                         360
Phe Phe Pro Gly Ser His Pro Val Arg Gly Val Gln Val Met Lys
                365
                                     370
                                                         375
Val Gly Lys Leu Gln Leu His Gln Gly Met Phe Pro Gln Ala Met
                380
                                     385
Lys Asn Leu Arg Leu Ala Phe Asp Ile Met Arg Val Thr His Gly
                395
                                     400
                                                         405
Arg Glu His Ser Leu Ile Glu Asp Leu Ile Leu Leu Glu Glu
                410
                                     415
                                                         420
Cys Asp Ala Asn Ile Arg Ala Ser
                425
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                                      10
Lys Arg Arg Glu Val Phe Arg Lys Ser Gly Ala Thr Cys Gly Arg
                                      25
                 20
Ser Asp Thr Tyr Tyr Gln Ser Pro Thr Gly
                                         Asp Arg Ile Arg Ser
                 35
                                      40
                                                           45
Lys Val Glu Leu Thr Arg Tyr Leu Gly Pro Ala Cys Asp Leu Thr
                 50
                                      55
                                                           60
Leu Phe Asp Phe Lys Gln Gly Ile Leu Cys
                                         Tyr Pro Ala Pro Lys
                                      70
                 65
Ala His Pro Val Ala Val Ala Ser Lys Lys
                                        Arg Lys Lys Pro Ser
                                      85
                 80
Arg Pro Ala Lys Thr Arg Lys Arg Gln Val Gly Pro Gln Ser Gly
                                     100
                                                          105
                 95
Glu Val Arg Lys Glu Ala Pro Arg Asp Glu Thr Lys Ala Asp
                                                          Thr
                                     115
                                                          120
                110
Asp Thr Ala Pro Ala Ser Phe Pro Ala Pro Gly Cys Cys Glu Asn
                                     130
                125
Cys Gly Ile Ser Phe Ser Gly Asp Gly Thr Gln Arg Gln Arg Leu
                                     145
                                                          150
                140
Lys Thr Leu Cys Lys Asp Cys Arg Ala Gln Arg Ile Ala Phe Asn
                155
                                     160
                                                          165
Arg Glu Gln Arg Met Phe Lys Arg Val Gly Cys Gly Glu Cys
                                                         Ala
                                    175
                170
Ala Cys Gln Val Thr Glu Asp Cys Gly Ala Cys Ser Thr Cys Leu
                                    190
                185
                                                         195
Leu Gln Leu Pro His Asp Val Ala Ser Gly Leu Phe Cys Lys Cys
                200
                                    205
                                                         210
Glu Arg Arg Cys Leu Arg Ile Val Glu Arg Ser Arg Gly Cys
                215
                                    220
                                                         225
Gly Val Cys Arg Gly Cys Gln Thr Gln Glu Asp Cys Gly His Cys
                                    235
                                                         240
                230
Pro Ile Cys Leu Arg Pro Pro Arg Pro Gly Leu Arg Arg Gln Trp
```

250

```
Lys Cys Val Gln Arg Arg Cys Leu Arg Gly Lys His Ala Arg Arg
                 260
                                      265
                                                          270
Lys Gly Gly Cys Asp Ser Lys Met Ala Ala Arg Arg Pro Gly
                 275
                                      280
                                                          285
Ala Gln Pro Leu Pro Pro Pro Pro Ser Gln Ser Pro Glu Pro
                 290
                                      295
                                                          300
Thr Glu Pro His Pro Arg Ala Leu Ala Pro Ser Pro Pro Ala Glu
                 305
                                      310
                                                          315
Phe Ile Tyr Tyr Cys Val Asp Glu Asp Glu Leu Gln Pro Tyr Thr
                 320
                                      325
Asn Arg Arg Gln Asn Arg Lys Cys Gly Ala Cys Ala Ala Cys Leu
                 335
                                      340
                                                          345
Arg Arg Met Asp Cys Gly Arg Cys Asp Phe Cys Cys Asp Lys Pro
                 350
                                      355
                                                          360
Lys Phe Gly Gly Ser Asn Gln Lys Arg Gln Lys Cys Arg Trp Arg
                 365
                                      370
                                                          375
Gln Cys Leu Gln Phe Ala Met Lys Arg Leu Leu Pro Ser Val Trp
                 380
                                      385
                                                          390
Ser Glu Ser Glu Asp Gly Ala Gly Ser Pro Pro Pro Tyr Arg Arg
                 395
                                      400
                                                          405
Arg Lys Arg Pro Ser Ser Ala Arg Arg His His Leu Gly Pro Thr
                410
                                      415
                                                          420
Leu Lys Pro Thr Leu Ala Thr Arg Thr Ala Gln Pro Asp His Thr
                 425
                                     430
                                                          435
Gln Ala Pro Thr Lys Gln Glu Ala Gly Gly Gly Phe Val Leu Pro
                440
                                     445
                                                          450
Pro Pro Gly Thr Asp Leu Val Phe Leu Arg Glu Gly Ala Ser Ser
                 455
                                      460
Pro Val Gln Val Pro Gly Prc Val Ala Ala Ser Thr Glu Ala Leu
                470
                                     475
Leu Gln Val Lys Gln Glu Lys Ala Asp Thr Gln Asp Glu Trp Thr
                                     490
                485
                                                          495
Pro Gly Thr Ala Val Leu Thr Ser Pro Val Leu Val Pro Gly
                                                         Cys
                                     505
                500
                                                          510
Pro Ser Lys Ala Val Asp Pro Gly Leu Pro Ser Val Lys Gln Glu
                515
                                     520
Pro Pro Asp Pro Glu Glu Asp Lys Glu Glu Asn Lys Asp Asp Ser
                530
                                     535
                                                         540
Ala Ser Lys Leu Ala Pro Glu Glu Glu Ala Gly Gly Ala Gly Thr
                                     550
                545
Pro Val Ile Thr Glu Ile Phe Ser Leu Gly Gly Thr Arg Phe Arg
                560
                                     565
                                                         570
Asp Thr Ala Val Trp Leu Pro Arg Ser Lys Asp Leu Lys Lys Pro
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                                     580
Gly Ala Arg Lys Gln
                590
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<223> Incyte ID No.: 1685494CD1

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Leu Lys Lys Glu Gly Leu Arg Val Val Arg Glu Asp His Tyr Ser Thr Trp Glu Gln Gly Phe Lys Leu Gln Gly Asn Ser Lys Gly Leu Gly Gln Glu Pro Leu Cys Lys Gln Phe Arg Gln Leu Arg Tyr Glu Glu Thr Thr Gly Pro Arg Glu Ala Leu Ser Arg Leu Arg Glu Leu Cys Gln Gln Trp Leu Gln Pro Glu Thr His Thr Lys Glu Gln Ile Leu Glu Leu Leu Val Leu Glu Gln Phe Leu Ile Ile Leu Pro Lys Glu Leu Gln Ala Arg Val Gln Glu His His Pro Glu Ser Arg Glu Asp Val Val Val Leu Glu Asp Leu Gln Leu Asp Leu Gly Glu Thr Gly Gln Gln Val Asp Pro Asp Gln Pro Lys Lys Gln Lys Ile Leu Val Glu Glu Met Ala Pro Leu Lys Gly Val Gln Glu Gln Gln Val Arg His Glu Cys Glu Val Thr Lys Pro Glu Lys Glu Lys Gly Glu Glu Thr Arg Ile Glu Asn Gly Lys Leu Ile Val Val Thr Asp Ser Cys Gly Arg Val Glu Ser Ser Gly Lys Ile Ser Glu Pro Met Glu Ala His Asn Glu Gly Ser Asn Leu Glu Arg His Gln Ala Lys Pro Lys Glu Lys Ile Glu Tyr Lys Cys Ser Glu Arg Glu Gln Arg Phe Ile Gln His Leu Asp Leu Ile Glu His Ala Ser Thr His Thr Gly Lys Lys Leu Cys Glu Ser Asp Val Cys Gln Ser Ser Ser Leu Thr Gly His Lys Lys Val Leu Ser Arg Glu Lys Gly His Gln Cys His Glu Cys Gly Lys Ala Phe Gln Arg Ser Ser His Leu Val Arg His Gln Lys Ile His Leu Gly Glu Lys Pro Tyr Gln Cys Asn Glu Cys Gly Lys Val Phe Ser Gln Asn Ala Gly Leu Leu Glu His Leu Arg Ile His Thr Gly Glu Lys Pro Tyr Leu Cys Ile His Cys Gly Lys Asn Phe Arg Arg Ser Ser His Leu Asn Arg His Gln Arg Ile His Ser Gln Glu Glu Pro Cys Glu Cys Lys Glu Cys Gly Lys Thr Phe Ser Gln Ala Leu Leu Thr His His Gln Arg Ile His Ser His Ser Lys Ser His Gln Cys Asn Glu Cys Gly Lys Ala Phe Ser Leu Thr Ser Asp Leu Ile Arg His His Arg Ile His Thr Gly Glu Lys Pro Phe Lys Cys Asn Ile Cys Gln Lys Ala Phe Arg Leu Asn Ser His Leu Ala Gln His Val Arg Ile His Asn Glu Glu Lys Pro Tyr Gln Cys Ser Glu Cys Gly Glu Ala Phe Arg Gln Arg Ser Gly Leu Phe Gln His Gln Arg Tyr His His Lys Asp Lys Leu Ala

470 475

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<213> Homo sapiens
<220>
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Met Glu Ala Val Tyr Leu Val Val Asn Gly Leu Gly Leu Val Leu
                  5
                                       10
Asp Val Leu Thr Leu Val Leu Asp Leu Asn Phe Leu Leu Val Ser
                                      25
                 20
Ser Leu Leu Ala Ser Leu Ala Trp Leu Leu Ala Phe Val Tyr Asn
                                      40
                 35
Leu Pro His Thr Val Leu Thr Ser Leu Leu His Leu Gly Arg Gly
                                                           60
                                      55
                 50
Val Leu Leu Ser Leu Leu Ala Leu Ile Glu Ala Val Val Arg Phe
                                                           75
                                      70
                 65
Thr Cys Gly Gly Leu Gln Ala Leu Cys Thr Leu Leu Tyr Ser Cys
                                                           90
                                      85
                 80
Cys Ser Gly Leu Glu Ser Leu Lys Leu Leu Gly His Leu Ala Ser
                                     100
                 95
His Gly Ala Leu Arg Ser Arg Glu Ile Leu His Arg Gly Val Leu
                                     115
                                                          120
                110
Asn Val Val Ser Ser Gly His Ala Leu Leu Arg Gln Ala Cys Asp
                                                          135
                125
                                     130
Ile Cys Ala Ile Ala Met Ser Leu Val Ala Tyr Val Ile Asn Ser
                                     145
                140
                                                          150
Leu Val Asn Ile Cys Leu Ile Gly Thr Gln Asn Leu Phe Ser Leu
                                     160
                155
Val Leu Ala Leu Trp Asp Ala Val Thr Gly Pro Leu Trp Arg Met
                                     175
                170
Thr Asp Val Val Ala Ala Phe Leu Ala His Ile Ser Ser Ala
                                     190
                                                          195
                185
Val Ala Met Ala Ile Leu Leu Trp Thr Pro Cys Gln Leu Ala Leu
                                     205
                                                          210
                200
Glu Leu Leu Ala Ser Ala Ala Arg Leu Leu Ala Ser Phe Val Leu
                                     220
                215
Val Asn Leu Thr Gly Leu Val Leu Leu Ala Cys Val Leu Ala Val
                                                          240
                230
                                     235
Thr Val Thr Val Leu His Pro Asp Phe Thr Leu Arg Leu Ala Thr
                245
                                     250
                                                          255
Gln Ala Leu Ser Gln Leu His Ala Arg Pro Ser Tyr His Arg Leu
                                     265
                260
Arg Glu Asp Val Met Arg Leu Ser Arg Leu Ala Leu Gly Ser Glu
                                     280
                                                          285
                275
Ala Trp Arg Arg Val Trp Ser Arg Ser Leu Gln Leu Ala Ser Trp
                                     295
                                                          300
                290
Pro Asn Arg Gly Gly Ala Pro Gly Ala Pro Gln Gly Asp Pro Met
                                     310
                305
Arg Val Phe Ser Val Arg Thr Arg Arg Gln Asp Thr Leu Pro Glu
                                                          330
                320
                                     325
Ala Gly Arg Arg Ser Glu Ala Glu Glu Glu Glu Ala Arg Thr Ile
                335
                                     340
Arg Val Thr Pro Val Arg Gly Arg Glu Arg Leu Asn Glu Glu Glu
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```
350
                                    355
                                                         360
Pro Pro Gly Gln Asp Pro Trp Lys Leu Leu Lys Glu Gln Glu
                365
                                    370
                                                         375
Glu Arg Lys Lys Cys Val Ile Cys Gln Asp Gln Ser Lys Thr Val
                380
                                    385
Leu Leu Pro Cys Arg His Leu Cys Leu Cys Gln Ala Cys Thr
                395
                                                         405
                                    400
Glu Ile Leu Met Arg His Pro Val Tyr His Arg Asn Cys Pro Leu
                410
                                    415
                                                         420
Cys Arg Arg Gly Ile Leu Gln Thr Leu Asn Val Tyr Leu
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Met Pro Lys Lys Lys Thr Gly Ala Arg Lys Lys Ala Glu Asn Arg
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Arg Glu Arg Glu Lys Gln Leu Arg Ala Ser Arg Ser Thr Ile Asp
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                                                           30
                                      25
Leu Ala Lys His Pro Cys Asn Ala Ser Met Glu Cys Asp Lys Cys
                 35
                                      40
                                                           45
Gln Arg Arg Gln Lys Asn Arg Ala Phe Cys Tyr Phe Cys Asn Ser
                 50
                                      55
Val Gln Lys Leu Pro Ile Cys Ala Gln Cys Gly Lys Thr Lys Cys
                 65
                                      70
Met Met Lys Ser Ser Asp Cys Val Ile Lys His Ala Gly Val
                                                          Tyr
                                      85
                                                           90
                 80
Ser Thr Gly Leu Ala Met Val Gly Ala Ile Cys Asp Phe Cys Glu
                 95
                                    100
                                                          105
Ala Trp Val Cys His Gly Arg Lys Cys Leu Ser Thr His Ala Cys
                                                          120
                110
                                     115
Ala Cys Pro Leu Thr Asp Ala Glu Cys Val Glu Cys Glu Arg Gly
                                    130
                125
Val Trp Asp His Gly Gly Arg Ile Phe Ser Cys Ser Phe Cys His
                                    145
                140
                                                         150
Asn Phe Leu Cys Glu Asp Asp Gln Phe Glu His Gln Ala Ser Cys
                155
                                    160
                                                          165
Gln Val Leu Glu Ala Glu Thr Phe Lys Cys Val Ser Cys Asn Arg
                                    175
                170
Leu Gly Gln His Ser Cys Leu Arg Cys Lys Ala Cys Phe Cys Asp
                                    190
                                                         195
                185
Asp His Thr Arg Ser Lys Val Phe Lys Gln Glu Lys Gly Lys Gln
                200
                                    205
                                                         210
Pro Pro Cys Pro Lys Cys Gly His Glu Thr Gln Glu Thr Lys
                                                         Asp
                215
                                    220
Leu Ser Met Ser Thr Arg Ser Leu Lys Phe Gly Arg Gln Thr Gly
                                    235
                                                         240
                230
Gly Glu Glu Gly Asp Gly Ala Ser Gly Tyr Asp Ala Tyr Trp Lys
                245
                                    250
                                                         255
Asn Leu Ser Ser Asp Lys Tyr Gly Asp Thr Ser Tyr His Asp Glu
                260
                                    265
Glu Glu Asp Glu Tyr Glu Ala Glu Asp Asp Glu Glu Glu Asp
```

285

WO 00/44900 PCT/US00/02237

280

```
Glu Gly Arg Lys Asp Ser Asp Thr Glu Ser Ser Asp Leu Phe Thr
                 290
                                      295
Asn Leu Asn Leu Gly Arg Thr Tyr Ala Ser Gly Tyr Ala His Tyr
                 305
                                      310
                                                          315
Glu Glu Gln Glu Asn
                 320
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Met Ala Ala Gly Phe Phe Gln Pro Phe Met Ser Pro Arg Phe Pro
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Gly Gly Pro Arg Pro Thr Leu Arg Met Pro Ser Gln Pro Pro Ala
                  20
                                       25
Cys Leu Pro Gly Ser Gln Pro Leu Leu Pro Gly Ala Met Glu Pro
                  35
                                      40
Ser Pro Arg Ala Gln Gly His Pro Ser Met Gly Gly Pro Met Gln
                                      55
                  50
                                                           60
Arg Val Thr Pro Pro Arg Gly Met Ala Ser Val Gly Pro Gln Ser
                  65
                                      70
Tyr Gly Gly Met Arg Pro Pro Pro Asn Ser Leu Ala Gly Pro
                 80
                                      85
Gly Leu Pro Ala Met Asn Met Gly Pro Gly Val Arg Gly Pro Trp
                 95
                                     100
                                                         105
Ala Ser Pro Ser Gly Asn Ser Ile Pro Tyr Ser Ser Ser Pro
                110
                                     115
                                                         120
Gly Ser Tyr Thr Gly Pro Pro Gly Gly Gly Pro Pro Gly Thr
                125
                                     130
Pro Ile Met Pro Ser Pro Gly Asp Ser Thr Asn Ser Ser Glu Asn
                140
                                     145
Met Tyr Thr Ile Met Asn Pro Ile Gly Gln Gly Ala Gly Arg Ala
                155
                                     160
Asn Phe Pro Leu Gly Pro Gly Pro Glu Gly Pro Trp Pro Pro
                170
                                     175
<210> 17
<211> 494
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<223> Incyte ID No.: 2445008CD1
<400> 17
Met Gly Arg Lys Lys Lys Gln Leu Lys Pro Trp Cys Trp Tyr
                  5
                                     10
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275

20/91

Cys Asn Arg Asp Phe Asp Asp Glu Lys Ile Leu Ile Gln His Gln

## PCT/US00/02237

wo	00.	/44	90	10
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Lys	Ala	Lys	His		Lys	Суз	His	Ile	25 Cys	His	Lys	Lys	Leu	30 Tyr
Thr	Gly	Pro	Gly		Ala	Ile	His	Cys	40 Met	Gln	Val	His	Lys	45 Glu 60
Thr	Ile	Asp	Ala		Pro	Asn	Ala	Ile	55 Pro 70	Gly	Arg	Thr	Asp	
Glu	Leu	Glu	Ile	65 Tyr 80	Gly	Met	Glu	Gly		Pro	Glu	Lys	Asp	
Asp	Glu	Arg	Arg		Leu	Leu	Glu	Gln		Thr	Gln	Glu	Ser	
Lys	Lys	Lys	Gln		Asp	Asp	Ser	Asp	Glu 115	Tyr	Asp	Asp	Asp	Asp 120
				125					130				Pro	135
				140					145				Pro	150
				155					160				Met	165
				170					175				Pro	180
				185					190				Ser	195
				200					205				Pro	210
				215					220				Gly	225
				230					235				Gln	240
				245					250				Ala	255
				260					265				Pro Ser	270
-				275					280				Lys	285
				290					295				Gly	300
				305					310				Thr	315
				320					325				Ser	330
				335					340				Pro	345
				350					355				Ser	360
				365					370				Glu	375
				380					385				Arg	390
				395					400					405
				410					415				Gly	420
				425					430				Met	435
				Pro 440					445				Gln	450
				455					460				Gln	465
Pro	Pro	Met	Val	Pro 470	Pro	Tyr	Gln	Gly	Gly 475	Pro	Pro	Arg	Pro	Pro 480

21/91

大學一個大學主義主義 经收入的经济基础 化水流管 经收益额 医水杨醇 医克斯特氏征 电电路 医电路 医电路 医二甲二甲基甲甲基甲基

Met Gly Met Arg Pro Pro Val Met Ser Gln Gly Gly Arg Tyr 485 490

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<210> 18
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<213> Homo sapiens
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Met Ala Ser Ser Pro Arg Pro Lys Met Asp Ala Ile Leu Thr Glu
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Ala Ile Lys Ala Cys Phe Gln Lys Ser Gly Ala Ser Val Val Ala
                  20
                                       25
                                                            30
Ile Arg Lys Tyr Ile Ile His Lys Tyr Pro Ser Leu Glu Leu Glu
                  35
                                       40
                                                            45
Arg Arg Gly Tyr Leu Leu Lys Gln Ala Leu Lys Arg Glu Leu Asn
                  50
                                       55
                                                            60
Arg Gly Val Ile Lys
                    Gln Val Lys Gly Lys Gly Ala Ser Gly Ser
                  65
                                       70
Phe Val Val Val Gln Lys Ser Arg Lys Thr Pro Gln Lys Ser Arg
                  80
                                       85
                                                            90
Asn Arg Lys Asn Arg Ser Ser Ala Val Asp
                                         Pro Glu Pro Gln Val
                  95
                                     100
Lys Leu Glu Asp Val Leu Pro Leu Ala Phe Thr Arg Leu Cys Glu
                110
                                     115
                                                           120
Pro Lys Glu Ala Ser Tyr Ser Leu Ile Arg Lys Tyr Val Ser Gln
                125
                                     130
                                                           135
Tyr Tyr Pro Lys Leu Arg Val Asp Ile Arg Pro Gln Leu Leu Lys
                140
                                     145
Asn Ala Leu Gln Arg Ala Val Glu Arg Gly Gln Leu Glu Gln Ile
                155
                                     160
                                                          165
Thr Gly Lys Gly Ala Ser Gly Thr Phe Gln Leu Lys Lys Ser Gly
                170
                                     175
                                                          180
Glu Lys Pro Leu Leu Gly Gly Ser Leu Met Glu Tyr Ala Ile Leu
                185
                                     190
Ser Ala Ile Ala Ala Met Asn Glu Pro Lys Thr Cys Ser Thr Thr
                200
                                     205
                                                          210
Ala Leu Lys Lys Tyr Val Leu Glu Asn His Pro Gly Thr Asn
                215
                                     220
                                                          225
Asn Tyr Gln Met His Leu Leu Lys Lys Thr Leu Gln Lys Cys Glu
                230
                                     235
                                                          240
Lys Asn Gly Trp Met Glu Gln Ile Ser Gly
                                         Lys Gly Phe Ser Gly
                245
                                     250
Thr Phe Gln Leu Cys Phe Pro Tyr Tyr Pro Ser Pro Gly Val Leu
                260
                                     265
Phe Pro Lys Lys Glu Pro Asp Asp Ser Arg Asp Glu Asp Glu Asp
                275
                                     280
                                                          285
Glu Asp Glu Ser Ser Glu Glu Asp Ser Glu Asp Glu Glu Pro Pro
                290
                                     295
                                                          300
Pro Lys Arg Arg Leu Gln Lys Lys Thr Pro Ala Lys Ser Pro Gly
                305
                                     310
                                                          315
Lys Ala Ala Ser Val Lys Gln Arg Gly Ser Lys Pro Ala Pro Lys
                320
                                     325
                                                          330
Val Ser Ala Ala Gln Arg Gly Lys Ala Arg Pro Leu Pro Lys Lys
                335
                                     340
                                                          345
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22/91

\$2. 体髓/用品数 (3. %) [[[[[[]]]]] [[[]] [[]]

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                                      10
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Lys Pro Asn Tyr Ser Glu Leu Gln Asp Ser Asn Pro Glu Phe Thr
                  20
                                      25
Phe Gln Gln Pro Tyr Asp Gln Ala His Leu Leu Ala Ala Ile Pro
                  35
                                      40
Pro Pro Glu Ile Leu Asn Pro Thr Ala Ser Leu Pro Met Leu Ile
                  50
                                      55
Trp Asp Ser Val Leu Ala Pro Gln Ala Gln Pro Ile Ala Trp Ala
                                      70
                  65
                                                           75
Ser Leu Arg Leu Gln Glu Ser Pro Arg Val Ala Glu Leu Thr Ser
                                                           90
                  80
                                      85
Leu Ser Asp Glu Asp Ser Gly Lys Gly Ser Gln Pro Pro Ser Pro
                  95
                                     100
                                                          105
Pro Ser Pro Ala Pro Ser Ser Phe Ser Ser Thr Ser Ala Ser Ser
                110
                                     115
Leu Glu Ala Glu Ala Tyr Ala Ala Phe Pro Gly Leu Gly Gln Val
                125
                                     130
                                                          135
Pro Lys Gln Leu Ala Gln Leu Ser Glu Ala Lys Asp Leu Gln Ala
                                     145
                140
                                                          150
Arg Lys Ala Phe Asn Cys Lys Tyr Cys Asn Lys Glu Tyr Leu Ser
                155
                                     160
                                                          165
Leu Gly Ala Leu Lys Met His Ile Arg Ser His Thr Leu Pro Cys
                                     175
                                                          180
                170
Val Cys Gly Thr Cys Gly Lys Ala Phe Ser Arg Pro Trp Leu Leu
                                     190
                185
Gln Gly His Val Arg Thr His Thr Gly Glu Lys Pro Phe Ser Cys
                200
                                     205
                                                         210
Pro His Cys Ser Arg Ala Phe Ala Asp Arg Ser Asn Leu Arg Ala
                215
                                     220
                                                         225
His Leu Gln Thr His Ser Asp Val Lys Lys Tyr Gln Cys Gln Ala
                230
                                     235
                                                         240
Cys Ala Arg Thr Phe Ser Arg Met Ser Leu Leu His Lys His Gln
                245
                                     250
Glu Ser Gly Cys Ser Gly Cys Pro Arg
                260
```

PCT/US00/02237

WO 00/44900

<210> 21

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<210> 20
<211> 153
<212> PRT
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                                      10
Glu Ala Cys Ser Gly Glu Arg Thr Tyr Gln Glu Leu Leu Val Asn
                 20
                                      25
                                                           30
Gln Asn Pro Ile Ala Gln Pro Leu Ala Ser Arg Arg Leu Thr Arg
                                      40
                                                           45
                 35
Lys Leu Tyr Lys Cys Ile Lys Lys Ala Val Lys Gln Lys Gln Ile
                                      55
                 50
Arg Arg Gly Val Lys Glu Val Gln Lys Phe Val Asn Lys Gly Glu
                 65
                                      70
Lys Gly Ile Met Val Leu Ala Gly Asp Thr Leu Pro Ile Glu Val
                                                           90
                 80
                                      85
Tyr Cys His Leu Pro Val Met Cys Glu Asp Arg Asn Leu Pro Tyr
                                     100
                                                          105
                 95
Val Tyr Ile Pro Ser Lys Thr Asp Leu Gly Ala Ala Ala Gly Ser
                                     115
                110
Lys Arg Pro Thr Cys Val Ile Met Val Lys Pro His Glu Glu Tyr
                                                          135
                125
                                     130
Gln Glu Ala Tyr Asp Glu Cys Leu Glu Glu Val Gln Ser Leu Pro
                140
                                     145
Leu Pro Leu
```

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<212> PRT
<213> Homo sapiens
<220>
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Met Gly Asp Asp Ile Ser Thr His Ile Ala Pro Lys Glu Leu Arg
                                      10
His Lys His Pro Ser Ser Val Asp Glu Val Ala Gln Val Val Lys
                                                           30
                 20
                                      25
Gln Leu Arg Ile Ile Leu Gln Gln Gln Val Arg Pro Gly Glu Ser
                                                           45
                 35
Thr Val Leu Ala Leu Arg Pro Asn Val Gln Gln Ile Glu Ala Pro
                                      55
                 50
Asp Val Ser Arg Asp Pro Arg Val Leu Gly Phe Asp Phe Pro Gly
                                      70
                                                           75
                 65
Ser Ala Arg Ile His Glu Gly Thr His Thr Leu Glu Lys Pro Tyr
                 80
                                      85
                                                           90
Glu Cys Lys Gln Cys Gly Lys Leu Leu Ser His Arg Ser Ser Phe
                 95
                                     100
Arg Arg His Met Met Ala His Thr Gly Asp Gly Pro His Lys Cys
                                                          120
                                     115
                110
Thr Val Cys Gly Lys Ala Phe Asp Ser Pro Ser Val Phe Gln Arg
```

```
130
                125
His Glu Arg Thr His Thr Gly Glu Lys Pro Tyr Glu Cys Lys Gln
                                     145
                140
Cys Gly Lys Ala Phe Arg Thr Ser Ser Leu Arg Lys His Glu
                                     160
                155
Thr Thr His Thr Gly Glu Gln Pro Tyr Lys Cys Lys Cys Gly Lys
                170
                                     175
Ala Phe Ser Asp Leu Phe Ser Phe Gln Ser His Glu Thr Thr His
                                     190
                                                          195
                1.85
Ser Glu Glu Glu Pro Tyr Glu Cys Lys Glu Cys Gly Lys Ala Phe
                200
                                     205
                                                          210
Ser Ser Phe Lys Tyr Phe Cys Arg His Glu Arg Thr His Ser Glu
                                     220
                215
Glu Lys Ser Tyr Glu Cys Gln Ile Cys Gly Lys Leu Ser Val Val
                                     235
                230
Ser Val Thr
```

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<210> 22
<211> 485
<212> PRT
<213> Homo sapiens
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<223> Incyte ID No.: 2960640CD1
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<400> 22 Met Arg Asp Asn Arg Ala Val Ser Leu Cys Gln Gln Glu Trp Met 10 Cys Pro Gly Pro Ala Gln Arg Ala Leu Tyr Arg Gly Ala Thr Gln 20 Arg Lys Asp Ser His Val Ser Leu Ala Thr Gly Val Pro Trp Gly 40 45 35 Tyr Glu Glu Thr Lys Thr Leu Leu Ala Ile Leu Ser Ser Ser Gln 50 55 60 Phe Tyr Gly Lys Leu Gln Thr Cys Gln Gln Asn Ser Gln Ile Tyr 65 70 Arg Ala Met Ala Glu Gly Leu Trp Glu Gln Gly Phe Leu Arg Thr 85 90 80 Pro Glu Gln Cys Arg Thr Lys Phe Lys Ser Leu Gln Leu Ser Tyr 105 95 100 Arg Lys Val Arg Arg Gly Arg Val Pro Glu Pro Cys Ile Phe Tyr 110 115 120 Glu Glu Met Asn Ala Leu Ser Gly Ser Trp Ala Ser Ala Pro Pro 125 130 Met Ala Ser Asp Ala Val Pro Gly Gln Glu Gly Ser Asp Ile Glu 145 140 Ala Gly Glu Leu Asn His Gln Asn Gly Glu Pro Thr Glu Val Glu 155 160 165 Asp Gly Thr Val Asp Gly Ala Asp Arg Asp Glu Lys Asp Phe Arg 175 170 Asn Pro Gly Gln Glu Val Arg Lys Leu Asp Leu Pro Val Leu Phe 190 185 Pro Asn Arg Leu Gly Phe Glu Phe Lys Asn Glu Ile Lys Lys Glu 200 205 210 Asn Leu Lys Trp Asp Asp Ser Glu Glu Val Glu Ile Asn Lys Ala 215 220 Leu Gln Arg Lys Ser Arg Gly Val Tyr Trp His Ser Glu Leu Gln

```
235
                230
                                                          240
Lys Gly Leu Glu Ser Glu Pro Thr Ser Arg Arg Gln Cys Arg Asn
                                     250
Ser Pro Gly Glu Ser Glu Glu Lys Thr Pro Ser Gln Glu Lys Met
                                     265
                260
                                                          270
Ser His Gln Ser Phe
                    Cys Ala Arg Asp Lys Ala Cys Thr His
                                                          Ile
                275
                                     280
                                                          285
Leu Cys Gly Lys Asn Cys Ser Gln Ser Val His Ser Pro His Lys
                290
                                     295
                                                          300
Pro Ala Leu Lys Leu Glu Lys Val Ser Gln Cys Pro Glu Cys Gly
                305
                                     310
                                                          315
Lys Thr Phe Ser Arg
                    Ser Ser Tyr Leu Val Arg His Gln Arg Ile
                320
                                     325
                                                          330
His Thr Gly Glu Lys Pro His Lys Cys Ser Glu Cys Gly Lys Gly
                335
                                     340
                                                          345
Phe Ser Glu Arg Ser Asn Leu Thr Ala His Leu Arg Thr His Thr
                350
                                     355
Gly Glu Arg Pro Tyr Gln Cys Gly Gln Cys Gly Lys Ser Phe Asn
                365
                                     370
Gln Ser Ser Leu Ile Val His Gln Arg Thr His Thr Gly Glu
                380
                                     385
                                                          390
Lys Pro Tyr Gln Cys
                    Ile Val Cys Gly Lys Arg Phe Asn Asn Ser
                                     400
                395
                                                          405
Ser Gln Phe Ser Ala His Arg Arg Ile His Thr Gly Glu Ser Pro
                410
                                     415
                                                          420
Tyr Lys Cys Ala Val Cys Gly Lys Ile Phe Asn Asn Ser Ser His
                425
                                     430
Phe Ser Ala His Arg Lys Thr His Thr Gly Glu Lys Pro Tyr Arg
                                     445
                440
                                                          450
Cys Ser His Cys Glu Arg Gly Phe Thr Lys Asn Ser Ala Leu Thr
                455
                                    460
                                                          465
Arg His Gln Thr Val His Met Lys Ala Val Leu Ser Ser Gln Glu
                470
                                    475
                                                          480
Gly Arg Asp Ala Leu
                485
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<210> 23
<211> 160
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 3454051CD1
<400> 23
Met Ser Trp Thr Cys Pro Arg Cys Gln Gln Pro Val Phe Phe Ala
Glu Lys Val Ser Ser Leu Gly Lys Asn Trp His Arg Phe Cys Leu
```

20

35

50

65

80

Lys Cys Glu Arg Cys His Ser Ile Leu Ser

Glu His Asn Gly Arg Pro Tyr Cys His Lys

26/91

的 1 稳定差别解数据储存剂 连闭新点性的

10

25

40

55

70

85

Leu Phe Gly Pro Arg Gly Pro Pro His Met Lys Thr Phe Thr Gly

Glu Thr Ser Leu Cys Pro Gly Cys Gly Glu Pro Val Tyr Phe Ala

30

60

75

Pro Gly Gly His Ala

Pro Cys Tyr Gly Ala

```
Glu Lys Val Met Ser Leu Gly Arg Asn Trp His Arg Pro Cys Leu 95 100 105

Arg Cys Gln Arg Cys His Lys Thr Leu Thr Ala Gly Ser His Ala 110 115 120

Glu His Asp Gly Val Pro Tyr Cys His Val Pro Cys Tyr Gly Tyr 125 130 135

Leu Phe Gly Pro Lys Gly Val Asn Ile Gly Asp Val Gly Cys Tyr 140 145 150

Ile Tyr Asp Pro Val Lys Ile Lys Phe Lys 160
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<210> 24
<211> 511
<212> PRT
<213> Homo sapiens
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<220>
<221>
<223> Incyte ID No.: 3510640CD1

Met Gln Glu Leu Tyr Ser Thr Pro Ala Ser Arg Leu Asp Ser Phe Val Ala Gln Trp Leu Gln Pro His Arg Glu Trp Lys Glu Glu Val Leu Asp Ala Val Arg Thr Val Glu Glu Phe Leu Arg Gln Glu His Phe Gln Gly Lys Arg Gly Leu Asp Gln Asp Val Arg Val Leu Lys Val Val Lys Val Gly Ser Phe Gly Asn Gly Thr Val Leu Arg Ser Thr Arg Glu Val Glu Leu Val Ala Phe Leu Ser Cys Phe His Ser Phe Gln Glu Ala Ala Lys His His Lys Asp Val Leu Arg Leu Ile Trp Lys Thr Met Trp Gln Ser Gln Asp Leu Leu Asp Leu Gly Leu Glu Asp Leu Arg Met Glu Gln Arg Val Pro Asp Ala Leu Val Phe Thr Ile Gln Thr Arg Gly Thr Ala Glu Pro Ile Thr Val Thr Ile Val Pro Ala Tyr Arg Ala Leu Gly Pro Ser Leu Pro Asn Ser Gln Pro Pro Pro Glu Val Tyr Val Ser Leu Ile Lys Ala Cys Gly Gly Pro Gly Asn Phe Cys Pro Phe Phe Ser Glu Leu Gln Arg Asn Phe Val Lys His Arg Pro Thr Lys Leu Lys Ser Leu Leu Arg Leu Val Lys His Trp Tyr Gln Gln Tyr Val Lys Ala Arg Ser Pro Arg Ala Asn Leu Pro Pro Leu Tyr Ala Leu Glu Leu Leu Thr Ile Tyr Ala Trp Glu Met Gly Thr Glu Glu Asp Glu Asn Phe Met Leu Asp Glu Gly Phe Thr Thr Val Met Asp Leu Leu Leu Glu Tyr Glu Val Ile Cys Ile Tyr Trp Thr Lys Tyr Tyr Thr Leu His Asn Ala Ile Ile

```
285
                                     280
                275
Glu Asp Cys Val Arg Lys Gln Leu Lys Lys Glu Arg Pro Ile Ile
                                     295
                290
Leu Asp Pro Ala Asp Pro Thr Leu Asn Val Ala Glu Gly Tyr Arg
                                                          315
                                     310
                305
Trp Asp Ile Val Ala Gln Arg Ala Ser Gln Cys Leu Lys Gln Asp
                                                          330
                                     325
                320
Cys Cys Tyr Asp Asn Arg Glu Asn Pro Ile Ser Ser Trp Asn Val
                                     340
                335
                    Ile His Leu Thr Val Glu Gln Arg Gly Tyr
Lys Arg Ala Arg Asp
                                                          360
                350
                                     355
Pro Asp Phe Asn Leu Ile Val Asn Pro Tyr Glu Pro Ile Arg Lys
                                     370
                                                          375
                365
                                         Tyr Ser Gly Leu Gln
Val Lys Glu Lys Ile Arg Arg Thr Arg Gly
                                     385
                380
Arg Leu Ser Phe Gln Val Pro Gly Ser Glu Arg Gln Leu Leu Ser
                                                          405
                                     400
                395
Ser Arg Cys Ser Leu Ala Lys Tyr Gly Ile Phe Ser His Thr His
                                                          420
                                     415
                410
Ile Tyr Leu Leu Glu Thr Ile Pro Ser Glu Ile Gln Val Phe Val
                                                          435
                                     430
                425
Lys Asn Pro Asp Gly Gly Ser Tyr Ala Tyr Ala Ile Asn Pro Asn
                                     445
                440
Ser Phe Ile Leu Gly Leu Lys Gln Gln Ile Glu Asp Gln Gln Gly
                455
                                     460
Leu Pro Lys Lys Gln Gln Gln Leu Glu Phe Gln Gly Gln Val Leu
                                     475
                470
Gln Asp Trp Leu Gly Leu Gly Ile Tyr Gly Ile Gln Asp Ser Asp
                                     490
                485
Thr Leu Ile Leu Ser Lys Lys Lys Gly Glu Ala Leu Phe Pro Ala
                                                          510
                                     505
                500
Ser
```

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<210> 25
<211> 310
<212> PRT
<213> Homo sapiens
<223> Incyte ID No.: 3815083CD1
<400> 25
Met Arg Pro Leu Gln Ile Val Pro Ser Arg Leu Ile Ser Gln Leu
                                                           15
                                      10
                  5
  1
Tyr Cys Gly Leu Lys Pro Pro Ala Ser Thr Arg Asn Gln Ile Cys
                                      25
                                                           30
                 20
Leu Lys Met Ala Arg Pro Ser Ser Ser Met Ala Asp Phe Arg Lys
                                                           45
                 35
                                      40
Phe Phe Ala Lys Ala Lys His Ile Val Ile Ile Ser Gly Ala Gly
                                                           60
                                      55
                 50
Val Ser Ala Glu Ser Gly Val Pro Thr Phe Arg Gly Ala Gly Gly
                                      70
                 65
Tyr Trp Arg Lys Trp Gln Ala Gln Asp Leu Ala Thr Pro Leu Ala
                                      85
                 80
Phe Ala His Asn Pro Ser Arg Val Trp Glu Phe Tyr His Tyr Arg
                                                          105
                                     100
                 95
Arg Glu Val Met Gly Ser Lys Glu Pro Asn Ala Gly His Arg Ala
```

28/91

```
Ile Ala Glu Cys Glu Thr Arg Leu Gly Lys Gln Gly Arg Arg Val
                125
                                     130
Val Val Ile Thr Gln Asn Ile Asp Glu Leu His Arg Lys Ala Gly
                                                          150
                                     145
                140
Thr Lys Asn Leu Leu Glu Ile His Gly Ser Leu Phe Lys Thr Arg
                155
                                     160
Cys Thr Ser Cys Gly Val Val Ala Glu Asn Tyr Lys Ser Pro Ile
                170
                                     175
Cys Pro Ala Leu Ser Gly Lys Gly Ala Pro Glu Pro Gly Thr Gln
                185
                                     190
                                                          195
Asp Ala Ser Ile Pro Val Glu Lys Leu Pro Arg Cys Glu Glu Ala
                                                          210
                200
                                     205
Gly Cys Gly Gly Leu Leu Arg Pro His Val Val Trp Phe Gly Glu
                215
                                     220
                                                          225
Asn Leu Asp Pro Ala Ile Leu Glu Glu Val Asp Arg Glu Leu Ala
                230
                                     235
His Cys Asp Leu Cys Leu Val Val Gly Thr Ser Ser Val Val Tyr
                                                          255
                245
                                     250
Pro Ala Ala Met Phe Ala Pro Gln Val Ala Ala Arg Gly Val Pro
                260
                                     265
                                                          270
Val Ala Glu Phe Asn Thr Glu Thr Thr Pro Ala Thr Asn Arg Phe
                275
                                     280
                                                          285
Arg Phe His Phe Gln Gly Pro Cys Gly Thr Thr Leu Pro Glu Ala
                290
                                     295
Leu Ala Cys His Glu Asn Glu Thr Val Ser
                305
<210> 26
<211> 331
<212> PRT
<213> Homo sapiens
<220> -
<221> misc-feature
<223> Incyte ID No.: 3988457CD1
Met Ala Ile Asn Arg Phe Arg Leu Glu Asn Asp Leu Glu Glu Leu
                                      10
Ala Leu Tyr Gln Ile Gln Leu Leu Lys Asp Leu Arg His Thr Glu
                 20
                                      25
Asn Glu Glu Asp Lys Val Ser Ser Ser Phe Arg Gln Arg Met
                 35
                                      40
Leu Gly Asn Leu Leu Arg Pro Pro Tyr Glu Arg Pro Glu Leu Pro
                                      55
                                                           60
Thr Cys Leu Tyr Val Ile Gly Leu Thr Gly
                                         Ile Ser Gly Ser Gly
                                      70
                 65
Lys Ser Ser Ile Ala Gln Arg Leu Lys Gly Leu Gly Ala Phe Val
                                      85
                 80
Ile Asp Ser Asp His Leu Gly His Arg Ala Tyr Ala Pro Gly Gly
                 95
                                     100
                                                         105
Pro Ala Tyr Gln Pro Val Val Glu Ala Phe Gly Thr Asp Ile Leu
                                     115
                110
His Lys Asp Gly Ile Ile Asn Arg Lys Val Leu Gly Ser Arg Val
                                                         135
                125
                                     130
Phe Gly Asn Lys Lys Gln Leu Lys Ile Leu Thr Asp Ile Met Trp
                                     145
                                                         150
                140
```

Pro Ile Ile Ala Lys Leu Ala Arg Glu Glu Met Asp Arg Ala Val

Ala Glu Gly Lys Arg Val Cys Val Ile Asp Ala Ala Val Leu Leu

29/91

```
Glu Ala Gly Trp Gln Asn Leu Val His Glu Val Trp Thr Ala Val
                185
                                     190
Ile Pro Glu Thr Glu Ala Val Arg Arg Ile Val Glu Arg Asp Gly
                200
                                     205
                                                          210
Leu Ser Glu Ala Ala Ala Gln Ser Arg Leu Gln Ser Gln Met Ser
                215
                                     220
                                                          225
Gly Gln Gln Leu Val Glu Gln Ser His Val Val Leu Ser Ser Pro
                230
                                     235
                                                          240
Cys Gly Ser Arg Ile Ser Pro Asn Ala Arg Trp Arg Lys Pro Gly
                245
                                     250
                                                          255
Pro Ser Cys Arg Ser Ala Phe Pro Arg Leu Ile Arg Pro Ser Thr
                260
                                     265
                                                          270
Glu Lys Phe Ser Val Gly Pro Asp Trp Leu Leu Glu Leu Thr Ser
                275
                                     280
                                                          285
Asp Pro Val Val Arg Arg Asn Gly Gly Leu Asp Ala His Pro Gly
                290
                                     295
                                                          300
Ser Gly Pro Glu Val Gln Ala Ile Leu Cys Arg Thr Trp Pro Gly
                305
                                     310
Leu Val Asp Thr Gly Ser Leu Pro Asn Thr Leu Val Phe Gly Gln
                320
His
```

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<210> 27
<211> 200
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 131890CD1
<400> 27
Met Met Thr Ala Glu Ser Arg Glu Ala Thr Gly Leu Ser Pro Gln
Ala Ala Gln Glu Lys Asp Gly Ile Val Ile Val Lys Val Glu Glu
                 20
```

25 Glu Asp Glu Glu Asp His Met Trp Gly Gln Asp Ser Thr Leu Gln 45 Asp Thr Pro Pro Pro Asp Pro Glu Ile Phe Arg Gln Arg Phe Arg 50 55 Arg Phe Cys Tyr Gln Asn Thr Phe Gly Pro Arg Glu Ala Leu Ser 65 70 Arg Leu Lys Glu Leu Cys His Gln Trp Leu Arg Pro Glu Ile Asn 80 85 Thr Lys Glu Gln Ile Leu Glu Leu Leu Val Leu Glu Gln Phe Leu 95 100 105 Ser Ile Leu Pro Lys Glu Leu Gln Val Trp Leu Gln Glu Tyr Arg 110 115 120 Pro Asp Ser Gly Glu Glu Ala Val Thr Leu Leu Glu Asp Leu Glu 125 130 135 Leu Asp Leu Ser Gly Gln Gln Val Pro Gly Gln Val His Gly Pro 140 145 Glu Met Leu Ala Arg Gly Met Val Pro Leu Asp Pro Val Gln Glu 155 160 Ser Ser Phe Asp Leu His His Glu Ala Thr Gln Ser His Phe 170 175 180 Lys His Ser Ser Arg Lys Pro Arg Leu Leu Gln Ser Arg Gly Lys 185 190 195 Lys Gln Gly Phe Ile

30/91

200

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<210> 28
<211> 100
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 238642CD1
<400> 28
Met Gln Lys Pro Cys Lys Glu Asn Glu Gly Lys Pro Lys Cys Ser
                                      10
  1
Val Pro Lys Arg Glu Glu Lys Arg Pro Tyr Gly Glu Phe Glu Arg
                 20
                                      25
Gln Gln Thr Glu Gly Asn Phe Arg Gln Arg Leu Leu Gln Ser Leu
                 35
                                      40
Glu Glu Phe Lys Glu Asp Ile Asp Tyr Arg His Phe Lys Asp Glu
                                      55
                 50
Glu Met Thr Arg Glu Gly Asp Glu Met Glu Arg Cys Leu Glu Glu
                                      70
                 65
Ile Arg Gly Leu Arg Lys Lys Phe Arg Ala Leu His Ser Asn His
                 80
                                      85
Arg His Ser Arg Asp Arg Pro Tyr Pro Ile
                 95
```

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<210> 29
<211> 528
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 669862CD1
<400> 29
Met Ser Ser Pro Tyr Pro Leu Leu Leu Glu Asn Ser Ile Cys Leu
                                      10
Phe Phe His Phe Leu Pro Asp Phe Asn Phe Thr Thr Glu Ser Asn
                                      25
                 20
Lys Leu Ser Ser Glu Lys Arg Asn Tyr Glu Val Asn Ala Tyr His
                 35
                                      40
Gln Glu Thr Trp Lys Arg Asn Lys Thr Phe Asn Leu Met Arg Phe
                                      55
Ile Phe Arg Thr Asp Pro Gln Tyr Thr Ile Glu Phe Gly Arg Gln
                                                          75
                 65
                                      70
Gln Arg Pro Lys Val Gly Cys Phe Ser Gln Met Ile Phe Lys Lys
                                                          90
                                      85
                 80
His Lys Ser Leu Pro Leu His Lys Arg Asn Asn Thr Arg Glu Lys
                 95
                                     100
                                                         105
Ser Tyr Glu Cys Lys Glu Tyr Lys Lys Gly Phe Arg Lys Tyr Leu
                                     115
                110
His Leu Thr Glu His Leu Arg Asp His Thr Gly Val Ile Pro Tyr
                                     130
                125
Glu Cys Asn Glu Cys Gly Lys Ala Phe Val Val Phe Gln His Phe
```

```
150
                140
                                     145
Ile Arg His Arg Lys Ile His Thr Asp Leu Lys Pro Tyr Glu Cys
                                                           165
                155
                    Ala Phe Arg Phe Tyr Ser Gln Leu Ile Gln
Asn Gly Cys Glu Lys
                                     175
                170
                                         Tyr Glu Cys Lys Gln
His Gln Ile Ile His
                    Thr Gly Met Lys Pro
                185
                                     190
                                                          195
Cys Gly Lys Ala Phe Arg Arg His Ser His Leu Thr Glu His Gln
                200
                                     205
                                                          210
Lys Ile His Val Gly
                    Leu Lys Pro Phe Glu Cys Lys Glu Cys Gly
                                     220
                215
Glu Thr Phe Arg Leu Tyr Arg His Met Cys Leu His Gln Lys Ile
                                                          240
                230
                                     235
His His Gly Val Lys Pro Tyr Lys Cys Lys Glu Cys Gly Lys Ala
                                     250
                                                          255
                245
Phe Gly His Arg Ser Ser Leu Tyr Gln His Lys Lys Ile His Ser
                260
                                     265
Gly Glu Lys Pro Tyr Lys Cys Glu Gln Cys Glu Lys Ala Phe Val
                                                          285
                                     280
                275
Arg Ser Tyr Leu Leu Val Glu His Gln Arg Ser His Thr Gly Glu
                290
                                     295
                                                          300
Lys Pro His Glu Cys Met Glu Cys Gly Lys Ala Phe Ser Lys Gly
                305
                                     310
                                                          315
Ser Ser Leu Leu Lys His Lys Arg Ile His Ser Ser Glu Lys Leu
                320
                                     325
                                                          330
                    Cys Gly Lys Ala Phe Cys Arg Gly Ser Gln
Tyr Asp Cys Lys Asp
                                     340
                335
Leu Thr Gln His Gln Arg Ile His Thr Gly
                                         Glu Lys Pro His Glu
                                                          360
                                     355
                350
Cys Lys Glu Cys Gly
                    Lys Thr Phe Lys Leu His Ser Tyr Leu Ile
                                                          375
                365
                                     370
                                         Pro Tyr Glu Cys
Gln His Gln Ile Ile
                    His Thr Asp Leu Lys
                                                         Lvs
                                                          390
                380
                                     385
Gln Cys Gly Lys Ala
                    Phe Ser Arg Val Gly Asp Leu Lys Thr His
                                     400
                395
Gln Ser Ile His Ala Gly Glu Lys Pro Tyr
                                         Glu Cys Lys Glu Cys
                                                          420
                410
                                     415
                                         Ile Tyr His Gln Thr
Gly Lys Thr Phe Arg Leu Asn Ser Gln Leu
                425
                                     430
                                                          435
Ile His Thr Gly Leu Lys Pro Tyr Val Cys Lys Glu Cys Lys Lys
                                     445
                440
Ala Phe Arg Ser Ile
                    Ser Gly Leu Ser Gln His Lys Arg Ile His
                455
                                     460
Thr Gly Glu Lys Pro Tyr Glu Cys Lys Glu Cys Asp Lys Ala Phe
                                                          480
                470
                                     475
Asn Arg Ser Asp Arg Leu Thr Gln His Glu Thr Ile His Thr Gly
                                                          495
                485
                                     490
Val Lys Pro Gln Lys Cys Lys Glu Cys Gly Lys Ala Phe Ser His
                                     505
                500
Cys Tyr Gln Leu Ser Gln His Gln Arg Phe His His Gly Glu Arg
                                                          525
                                     520
                515
Leu Leu Met
```

<sup>&</sup>lt;210> 30

<sup>&</sup>lt;211> 350

<sup>&</sup>lt;212> PRT

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;220>

<sup>&</sup>lt;221> misc-feature

<sup>&</sup>lt;223> Incyte ID No.: 1003663CD1

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<400> 30
Met His Pro Ala Ala Phe Pro Leu Pro Val Val Ala Ala Val
 1
Leu Trp Gly Ala Ala Pro Thr Arg Gly Leu Ile Arg Ala Thr Ser
                 20
                                      25
Asp His Asn Ala Ser Met Asp Phe Ala Asp Leu Pro Ala Leu Phe
                 35
                                      40
Gly Ala Thr Leu Ser Gln Glu Gly Leu Gln Gly Phe Leu Val Glu
                 50
                                      55
Ala His Pro Asp Asn Ala Cys Ser Pro Ile Ala Pro Pro Pro Pro
                                      70
                 65
                    Ser Val Phe Ile Ala Leu Leu Arg Arg Phe
Ala Pro Val Asn Gly
                                                           90
                 80
                                      85
                    Leu Lys Val Leu Asn Ala Gln Lys Ala Gly
Asp Cvs Asn Phe Asp
                                     100
                                                          105
                 95
Tyr Gly Ala Ala Val Val His Asn Val Asn Ser Asn Glu Leu Leu
                110
                                     115
Asn Met Val Trp Asn Ser Glu Glu Ile Gln Gln Gln Ile Trp Ile
                                                          135
                                     130
                125
Pro Ser Val Phe Ile Gly Glu Arg Ser Ser Glu Tyr Leu Arg Ala
                                                          150
                140
                                     145
Leu Phe Val Tyr Glu Lys Gly Ala Arg Val Leu Leu Val Pro Asp
                155
                                     160
                                                          165
Asn Thr Phe Pro Leu Gly Tyr Tyr Leu Ile Pro Phe Thr Gly Ile
                                     175
                                                          180
                170
Val Gly Leu Leu Val Leu Ala Met Gly Ala Val Met Ile Ala Arg
                                     190
                185
Cys Ile Gln His Arg Lys Arg Leu Gln Arg Asn Arg Leu Thr Lys
                                     205
                                                          210
                200
Glu Gln Leu Lys Gln Ile Pro Thr His Asp Tyr Gln Lys Gly Asp
                                                          225
                                     220
                215
                    Ala Ile Cys Leu Asp Glu Tyr Glu Asp Gly
Gln Tyr Asp Val Cys
                                     235
                                                          240
                230
Asp Lys Leu Arg Val Leu Pro Cys Ala His Ala Tyr His Ser Arg
                                     250
                245
Cys Val Asp Pro Trp Leu Thr Gln Thr Arg Lys Thr Cys Pro Ile
                                                          270
                260
                                     265
Cys Lys Gln Pro Val His Arg Gly Pro Gly Asp Glu Asp Gln Glu
                                                          285
                275
                                     280
Glu Glu Thr Gln Gly Gln Glu Glu Gly Asp Glu Gly Glu Pro Arg
                                     295
                                                          300
                290
Asp His Pro Ala Ser Glu Arg Thr Pro Leu Leu Gly Ser Ser Pro
                305
                                     310
Thr Leu Pro Thr Ser Phe Gly Ser Leu Ala Pro Ala Pro Leu Val
                                                         330
                320
                                     325
Phe Pro Gly Pro Ser Thr Asp Pro Pro Leu Ser Pro Pro Ser Ser
                                     340
                                                         345
                335
Pro Val Ile Leu Val
                350
```

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<210> 31
<211> 315
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
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<223> Incyte ID No.: 1432557CD1

WO 00/44900

PCT/US00/02237

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<400> 31
Met Ala Ala Leu Gly Val Leu Glu Ser Asp Leu Pro Ser Ala Val
                                      10
Thr Leu Leu Lys Asn Leu Gln Glu Gln Val Met Ala Val Thr Ala
                  20
                                      25
                                                           3.0
Gln Val Lys Ser Leu Thr Gln Lys Val Gln Ala Gly Ala Tyr Pro
                                      40
Thr Glu Lys Gly Leu Ser Phe Leu Glu Val Lys Asp Gln Leu Leu
                  50
                                      55
                                                           60
Leu Met Tyr Leu Met Asp Leu Thr His Leu Ile Leu Asp Lys Ala
                  65
                                      70
Ser Gly Gly Ser Leu Gln Gly His Asp Ala Val Leu Arg Leu Val
                  80
                                      85
Glu Ile Arg Thr Val Leu Glu Lys Leu Arg Pro Leu Asp Gln Lys
                  95
                                     100
                                                          105
Leu Lys Tyr Gln Ile Asp Lys Leu Ile Lys Thr Ala Val Thr Gly
                 110
                                     115
                                                          120
Ser Leu Ser Glu Asn Asp Pro Leu Arg Phe Lys Pro His Pro Ser
                 125
                                     130
Asn Met Met Ser Lys Leu Ser Ser Glu Asp Glu Glu Glu Asp Glu
                140
                                     145
                                                          150
Ala Glu Asp Asp Gln Ser Glu Ala Ser Gly Lys Lys Ser Val Lys
                155
                                     160
                                                          165
Gly Val Ser Lys Lys Tyr Val Pro Pro Arg Leu Val Pro Val His
                170
                                     175
                                                          180
Tyr Asp Glu Thr Glu Ala Glu Arg Glu Lys Lys Arg Leu Glu Arg
                185
                                     190
                                                         195
Ala Lys Arg Arg Ala Leu Ser Ser Ser Val Ile Arg Glu Leu Lys
                200
                                     205
                                                         210
Glu Gln Tyr Ser Asp Ala Pro Glu Glu Ile Arg Asp Ala Arg His
                215
                                     220
                                                         225
Pro His Val Thr Arg Gln Ser Gln Glu Asp Gln His Arg Ile Asn
                230
                                    235
                                                         240
Tyr Glu Glu Ser Met Met Val Arg Leu Ser Val Ser Lys Arg Glu
                245
                                    250
                                                         255
Lys Gly Arg Arg Lys Arg Ala Asn Val Met Ser Ser Gln Leu His
                260
                                    265
Ser Leu Thr His Phe Ser Asp Ile Ser Ala Leu Thr Gly Gly Thr
                275
                                    280
                                                         285
Val His Leu Asp Glu Asp Gln Asn Pro Ile Lys Lys Arg Lys Lys
                290
                                    295
                                                         300
Ile Pro Gln Lys Gly Arg Lys Lys Gly Phe Arg Arg Arg
                305
                                    310
```

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<210> 32
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<sup>&</sup>lt;211> 120

<sup>&</sup>lt;212> PRT

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;220>

<sup>&</sup>lt;221> misc-feature

<sup>&</sup>lt;223> 1441770CD1

<sup>&</sup>lt;400> 32

Met Asp Asp Ser Lys Val Val Gly Gly Lys Val Lys Lys Pro Gly

1 5 10 15

Lys Arg Gly Arg Lys Pro Ala Lys Ile Asp Leu Lys Ala Lys Leu

20 25 30

Glu Arg Ser Arg Gln Ser Ala Arg Glu Cys Arg Ala Arg Lys Lys

35 40 45

```
Leu Arg Tyr Gln Tyr Leu Glu Glu Leu Val Ser Ser Arg Glu Arg
                 50
                                      55
                                                           60
Ala Ile Cys Ala Leu Arg Glu Glu Leu Glu Met Tyr Lys Gln Trp
                 65
                                      70
                                                           75
Cys Met Ala Met Asp Gln Gly Lys Ile Pro Ser Glu Ile Lys Ala
                 80
                                      85
Leu Leu Thr Gly Glu Glu Gln Asn Lys Ser Gln Gln Asn Ser Ser
                 95
                                     100
                                                          105
Arg His Thr Lys Ala Gly Lys Thr Asp Ala Asn Ser Asn Ser Trp
                110
                                     115
```

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<210> 33
<211> 326
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 1456684CD1
<400> 33
Met Gln Glu Glu Pro Leu Pro Gln Gly Asn Asp Pro Glu Pro Ser
                   5
                                       10
                                                            15
Gly Asp Ser Pro Leu Gly Leu Cys Gln Ser Glu Cys Met Glu Met
                  20
                                       25
Ser Glu Val Phe Asp Asp Ala Ser Asp Gln Asp Ser Thr Asp Lys
                  35
                                       40
                                                            45
Pro Trp Arg Pro Tyr Tyr Asn Tyr Lys Pro Lys Lys Lys Ser Arg
                  50
                                       55
                                                            60
Gln Leu Lys Lys Met Arg Lys Val Asn Trp Arg Lys Glu His Gly
                 65
                                       70
                                                            75
Asn Arg Ser Pro Ser His Lys Cys Lys Tyr Pro Ala Glu Leu Asp
                 80
                                       85
                                                            90
Cys Ala Val Gly Lys Ala Pro Gln Asp Lys Pro Phe Glu Glu Glu
                 95
                                     100
                                                           105
Glu Thr Lys Glu Met Pro Lys Leu Gln Cys Glu Leu Cys Asp Gly
                110
                                     115
                                                           120
Asp Lys Ala Val Gly Ala Gly Asn Gln Gly Arg Pro His Arg His
                125
                                     130
Leu Thr Ser Arg Pro Tyr Ala Cys Glu Leu Cys Ala Lys Gln Phe
                140
                                     145
                                                          150
Gln Ser Pro Ser Thr Leu Lys Met His Met Arg Cys His Thr Gly
                155
                                     160
                                                          165
Glu Lys Pro Tyr Gln Cys Lys Thr Cys Gly Arg Cys Phe Ser Val
                170
                                     175
                                                          180
Gln Gly Asn Leu Gln Lys His Glu Arg Ile His Leu Gly Leu Lys
                185
                                     190
                                                          195
Glu Phe Val Cys Gln Tyr Cys Asn Lys Ala Phe Thr Leu Asn Glu
                200
                                     205
                                                          210
Thr Leu Lys Ile His Glu Arg Ile His Thr Gly Glu Lys Arg Tyr
                215
                                     220
                                                          225
His Cys Gln Phe Cys Phe Gln Arg Phe Leu Tyr Leu Ser Thr Lys
                230
                                     235
                                                          240
Arg Asn His Glu Gln Arg His Ile Arg Glu His Asn Gly Lys Gly
                245
                                     250
                                                          255
Tyr Ala Cys Phe Gln Cys Pro Lys Ile Cys Lys Thr Ala Ala Ala
                260
                                     265
                                                          270
Leu Gly Met His Gln Lys Lys His Leu Phe Lys Ser Pro Ser Gln
                275
                                     280
```

<210> 34

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Gln Glu Lys Ile Gly Asp Val Cys His Glu Asn Ser Asn Pro Leu 290 295 300
Glu Asn Gln His Phe Ile Gly Ser Glu Asp Asn Asp Gln Lys Asp 305 310 315
Asn Ile Gln Thr Gly Val Glu Asn Val Val Leu 320 325
```

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<211> 106
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 1602916CD1
<400> 34
Met Phe Pro Trp Met Arg Pro Gln Ala Ala Pro Gly Arg Arg Arg
 1
                                     10
                                                           15
Gly Arg Gln Thr Tyr Ser Arg Phe Gln Thr Leu Glu Leu Glu Lys
                 20
                                      25
Glu Phe Leu Phe Asn Pro Tyr Leu Thr Arg Lys Arg Arg Ile Glu
                 35
                                     40
Val Ser His Ala Leu Ala Leu Thr Glu Arg Gln Val Lys Ile Trp
                 50
                                     55
                                                           60
Phe Gln Asn Arg Arg Met Lys Trp Lys Lys Glu Asn Asn Lys Asp
                 65
                                     70
Lys Phe Pro Val Ser Arg Gln Glu Val Lys Asp Gly Glu Thr Lys
                                     85
                 80
Lys Glu Ala Gln Glu Leu Glu Glu Asp Arg Ala Glu Arg Leu Thr
                                    100
Asn
```

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<210> 35
<211> 209
<212> PRT '
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 1692816CD1
<400> 35
Met Asn Pro Ser Met Lys Gln Lys Gln Glu Glu Ile Lys Glu Asn
 1
                  5
                                      10
                                                           15
Ile Lys Asn Ser Ser Val Pro Arg Arg Thr Leu Lys Met Ile Gln
                 20
                                      25
                                                           30
Pro Ser Ala Ser Gly Ser Leu Val Gly Arg Glu Asn Glu Leu Ser
                 35
                                      40
Ala Gly Leu Ser Lys Arg Lys His Arg Asn Asp His Leu Thr Ser
                 50
                                      55
Thr Thr Ser Ser Pro Gly Val Ile Val Pro Glu Ser Ser Glu Asn
                 65
                                     70
Lys Asn Leu Gly Gly Val Thr Gln Glu Ser Phe Asp Leu Met Ile
                80
                                     85
Lys Glu Asn Pro Ser Ser Gln Tyr Trp Lys Glu Val Ala Glu Lys
```

#### PCT/US00/02237

#### WO 00/44900

<210> 36

```
105
                 95
                                     100
Arg Arg Lys Ala Leu Tyr Glu Ala Leu Lys Glu Asn Glu Lys Leu
                                     115
                110
His Lys Glu Ile Glu Gln Lys Asp Asn Glu Ile Ala Arg Leu Lys
                                                          135
                                     130
                125
Lys Glu Asn Lys Glu Leu Ala Glu Val Ala Glu His Val Gln Tyr
                                     145
                                                          150
                140
Met Ala Glu Leu Ile Glu Arg Leu Asn Gly Glu Pro Leu Asp Asn
                                     160
                155
Phe Glu Ser Leu Asp Asn Gln Glu Phe Asp Ser Glu Glu Glu Thr
                                     175
                170
Val Glu Asp Ser Leu Val Glu Asp Ser Glu Ile Gly Thr Cys Ala
                                     190
                                                          195
                185
Glu Gly Thr Val Ser Ser Ser Thr Asp Ala Lys Pro Cys Ile
                200
```

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<211> 212
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 1968191CD1
<400> 36
Met Leu Gly Asn Glu Trp Ser Lys Leu Pro Pro Glu Glu Lys Gln
Arg Tyr Leu Asp Glu Ala Asp Arg Asp Lys Glu Arg Tyr Met Lys
                                                           30
                                      25
                  20
Glu Leu Glu Gln Tyr Gln Lys Thr Glu Ala Tyr Lys Val Phe Ser
                  35
                                      40
Arg Lys Thr Gln Asp Arg Gln Lys Gly Lys Ser His Arg Gln Asp
                                                           60
                  50
                                      55
Ala Ala Arg Gln Ala Thr His Asp His Glu Lys Glu Thr Glu Val
                                      70
                                                           75
                  65
Lys Glu Arg Ser Val Phe Asp Ile Pro Ile Phe Thr Glu Glu Phe
                                      85
                  80
Leu Asn His Ser Lys Ala Arg Glu Ala Glu Leu Arg Gln Leu Arg
                                     100
                  95
Lys Ser Asn Met Glu Phe Glu Glu Arg Asn Ala Ala Leu Gln Lys
                                                          120
                                     115
                 110
His Val Glu Ser Met Arg Thr Ala Val Glu Lys Leu Glu Val Asp
                                     130
                 125
Val Ile Gln Glu Arg Ser Arg Asn Thr Val Leu Gln Gln His Leu
                                     145
                 140
Glu Thr Leu Arg Gln Val Leu Thr Ser Ser Phe Ala Ser Met Pro
                                                          165
                                     160
                 155
Leu Pro Gly Ser Gly Glu Thr Pro Thr Val Asp Thr Ile Asp Ser
                                                          180
                 170
                                     175
Tyr Met Asn Arg Leu His Ser Ile Ile Leu Ala Asn Pro Gln Asp
                                     190
                 185
Asn Glu Asn Phe Ile Ala Thr Val Arg Glu Val Val Asn Arg Leu
                                                          210
                 200
                                     205
Asp Arg
```

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<210> 37
<211> 359
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 2052061CD1
<400> 37
Met Val Asp Met Asp Lys Leu Ile Asn Asn Leu Glu Val Gln Leu
                                      10
Asn Ser Glu Gly Gly Ser Met Gln Val Phe Lys Gln Val Thr Ala
                 20
                                      25
Ser Val Arg Asn Arg Asp Pro Pro Glu Ile Glu Tyr Thr Ser Asn
                 35
                                      40
Met Thr Ser Pro Thr Leu Leu Asp Ala Asn Pro Met Glu Asn Pro
                 50
Ala Leu Phe Asn Asp Ile Lys Ile Glu Pro Pro Glu Glu Leu Leu
                                      70
                 65
Ala Ser Asp Phe Ser Leu Pro Gln Val Glu Pro Val Asp Leu Ser
                 80
                                      85
Phe His Lys Pro Lys Ala Pro Leu Gln Pro Ala Ser Met Leu Gln
                 95
                                     100
Ala Pro Ile Arg Pro Pro Lys Pro Gln Ser Ser Pro Gln Thr Leu
                                     115
                110
                                                          120
Val Val Ser Thr Ser Thr Ser Asp Met Ser Thr Ser Ala Asn Ile
                                     130
                                                          135
                125
Pro Thr Val Leu Thr Pro Gly Ser Val Leu Thr Ser Ser Gln Ser
                140
                                     145
                                                          150
Thr Gly Ser Gln Gln Ile Leu His Val Ile His Thr Ile Pro Ser
                155
                                     160
Val Ser Leu Pro Asn Lys Met Gly Gly Leu Lys Thr Ile Pro Val
                170
                                     175
Val Val Gln Ser Leu Pro Met Val Tyr Thr Thr Leu Pro Ala Asp
                185
                                     190
Gly Gly Pro Ala Ala Ile Thr Val Pro Leu Ile Gly Gly Asp Gly
                200
                                     205
                                                          210
Lys Asn Ala Gly Ser Val Lys Val Asp Pro Thr Ser Met Ser Pro
                                     220
                215
                                                          225
Leu Glu Ile Pro Ser Asp Ser Glu Glu Ser Thr Ile Glu Ser Gly
                                     235
                230
                                                          240
Ser Ser Ala Leu Gln Ser Leu Gln Gly Leu Gln Gln Glu Pro Ala
                245
                                     250
                                                          255
Ala Met Ala Gln Met Gln Gly Glu Glu Ser Leu Asp Leu Lys Arg
                260
                                     265
                                                          270
Arg Arg Ile His Gln Cys Asp Phe Ala Gly Cys Ser Lys Val Tyr
                                    280
                275
                                                          285
Thr Lys Ser Ser His Leu Lys Ala His Arg Arg Ile His Thr Gly
                                    295
                                                         300
                290
Glu Lys Pro Tyr Lys Cys Thr Trp Asp Gly Cys Ser Trp Lys Phe
                305
                                    310
                                                         315
Ala Arg Ser Asp Glu Leu Thr Arg His Phe Arg Lys His Thr Gly
                320
                                    325
                                                         330
Ile Lys Pro Phe Arg Cys Thr Asp Cys Asn Arg Ser Phe Ser Arg
                335
                                    340
Ser Asp His Leu Ser Leu His Arg Arg Arg His Asp Thr Met
                350
                                    355
```

38/91

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<211> 445
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 2056207CD1
<400> 38
Met Val Glu Cys Ile Arg Glu Val Asn Glu Val Ile Gln Asn Pro
                                       10
                                                           15
Ala Thr Ile Thr Arg Ile Leu Leu Ser His
                                         Phe Asn Trp Asp
                                                          Lys
                  20
                                       25
Glu Lys Leu Met Glu Arg Tyr Phe Asp Gly
                                         Asn Leu Glu Lys Leu
                                                           45
                  35
                                       40
Phe Ala Glu Cys His Val Ile Asn Pro Ser Lys Lys Ser Arg Thr
                  50
                                       55
                                                           60
Arg Gln Met Asn Thr Arg Ser Ser Ala Gln Asp Met Pro Cys Gln
                  65
                                       70
                                                           75
Ile Cys Tyr Leu Asn Tyr Pro Asn Ser Tyr
                                         Phe Thr Gly Leu Glu
                  80
                                       85
Cys Gly His Lys Phe Cys Met Gln Cys Trp
                                          Ser Glu Tyr Leu Thr
                                      100
                  95
Thr Lys Ile Met Glu Glu Gly Met Gly Gln Thr Ile Ser Cys Pro
                                                          120
                 110
                                      115
Ala His Gly Cys Asp Ile Leu Val Asp Asp Asn Thr Val Met Arg
                                      130
                 125
Leu Ile Thr Asp Ser Lys Val Lys Leu Lys
                                         Tyr Gln His Leu Ile
                 140
                                      145
Thr Asn Ser Phe Val Glu Cys Asn Arg Leu Leu Lys Trp Cys Pro
                 155
                                     160
                                                          165
Ala Pro Asp Cys His His Val Val Lys Val Gln Tyr Pro Asp Ala
                 170
                                     175
                                                          180
Lys Pro Val Arg Cys Lys Cys Gly Arg Gln Phe Cys Phe Asn Cys
                 185
                                     190
                                                          195
                                         Lys Trp Leu Lys Lys
Gly Glu Asn Trp His Asp Pro Val Lys Cys
                 200
                                     205
                                                          210
Trp Ile Lys Lys Cys Asp Asp Asp Ser Glu
                                         Thr Ser Asn Trp Ile
                                                          225
                 215
                                     220
Ala Ala Asn Thr Lys Glu Cys Pro Lys Cys His Val Thr Ile Glu
                                                          240
                 230
                                     235
Lys Asp Gly Gly Cys Asn His Met Val Cys Arg Asn Gln Asn Cys
                 245
                                     250
                                                          255
                    Trp Val Cys Leu Gly Pro Trp Glu Pro
                                                         His
Lys Ala Glu Phe Cys
                 260
                                     265
                                                          270
Gly Ser Ala Trp Tyr Asn Cys Asn Arg Tyr Asn Glu Asp Asp Ala
                                                          285
                                     280
                275
Lys Ala Ala Arg Asp Ala Gln Glu Arg Ser Arg Ala Ala Leu Gln
                 290
                                     295
                                                          300
Arg Tyr Leu Phe Tyr Cys Asn Arg Tyr Met Asn His Met Gln Ser
                305
                                     310
Leu Arg Phe Glu His Lys Leu Tyr Ala Gln Val Lys Gln Lys Met
                320
                                     325
                                                          330
Glu Glu Met Gln Gln His Asn Met Ser Trp Ile Glu Val Gln Phe
                335
                                     340
                                                          345
Leu Lys Lys Ala Val Asp Val Leu Cys Gln Cys Arg Ala Thr Leu
                350
                                     355
Met Tyr Thr Tyr Val Phe Ala Phe Tyr Leu Lys Lys Asn Asn Gln
                                                          375
                365
                                     370
Ser Ile Ile Phe Glu Asn Asn Gln Ala Asp Leu Glu Asn Ala Thr
                                     385
                                                          390
                380
```

<210> 38

39/91

WO 00/44900 PCT/US00/02237

```
420
                                     415
                410
Glu Ser Arg Arg Arg Val Leu Leu Gln His Val His Glu Gly Tyr
                                                          435
                425
                                     430
Glu Lys Asp Leu Trp Glu Tyr Ile Glu Asp
                440
<210> 39
<211> 433
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 2101803CD1
<400> 39
Met Arg Ala Glu Gly Leu Gly Leu Glu Arg Phe Cys Ser Pro
Gly Lys Gly Arg Gly Leu Arg Ala Leu Gln Pro Phe Gln Val Gly
                                      25
                 20
Asp Leu Leu Phe Ser Cys Pro Ala Tyr Ala
                                         Tyr Val Leu Thr Val
                                      40
                 35
Asn Glu Arg Gly Asn His Cys Glu Tyr Cys
                                         Phe Thr Arg Lys Glu
                                      55
                                                           60
                 50
Gly Leu Ser Lys Cys Gly Arg Cys Lys Gln Ala Phe Tyr Cys Asn
                                      70
                                                           75
                 65
Val Glu Cys Gln Lys Glu Asp Trp Pro Met His Lys Leu Glu Cys
                                                           90
                                      85
                 80
Ser Pro Met Val Val Phe Gly Glu Asn Trp Asn Pro Ser Glu Thr
                                                          105
                                     100
                 95
Val Arg Leu Thr Ala Arg Ile Leu Ala Lys Gln Lys Ile His Pro
                                     115
                                                          120
                110
Glu Arg Thr Pro Ser Glu Lys Leu Leu Ala Val Lys Glu Phe Glu
                                     130
                125
Ser His Leu Asp Lys Leu Asp Asn Glu Lys Lys Asp Leu Ile Gln
                                     145
                                                          150
                140
Ser Asp Ile Ala Ala Leu His His Phe Tyr Ser Lys His Leu Glu
                155
                                     160
                                                          165
Phe Pro Asp Asn Asp Ser Leu Val Val Leu Phe Ala Gln Val Asn
                                     175
                                                          180
                170
Cys Asn Gly Phe Thr Ile Glu Asp Glu Glu Leu Ser His Leu Gly
                                     190
                                                          195
                185
Ser Ala Ile Phe Pro Asp Val Ala Leu Met Asn His Ser Cys
                                                         Cvs
                                                          210
                                     205
                200
Pro Asn Val Ile Val Thr Tyr Lys Gly Thr Leu Ala Glu Val Arg
                                     220
                                                          225
                215
Ala Val Gln Glu Ile Lys Pro Gly Glu Glu Val Phe Thr Ser
                                                         Tvr
                                                          240
                230
                                     235
Ile Asp Leu Leu Tyr Pro Thr Glu Asp Arg Asn Asp Arg Leu Arg
                                                          255
                                     250
                245
Asp Ser Tyr Phe Phe Thr Cys Glu Cys Gln Glu Cys Thr Thr Lys
                                     265
                                                          270
                260
Asp Lys Asp Lys Ala Lys Val Glu Ile Arg Lys Leu Ser Asp Pro
```

Glu Val Leu Ser Gly Tyr Leu Glu Arg Asp Ile Ser Gln Asp Ser

Leu Gln Asp Ile Lys Gln Lys Val Gln Asp Lys Tyr Arg Tyr Cys

40/91

Pro Lys Ala Glu Ala Ile Arg Asp Met Val Arg Tyr Ala Arg Asn

```
Val Ile Glu Glu Phe Arg Arg Ala Lys His Tyr Lys Ser Pro Ser
                305
                                     310
Glu Leu Leu Glu Ile Cys Glu Leu Ser Gln Glu Lys Met Ser Ser
                320
                                      325
                                                          330
Val Phe Glu Asp Ser Asn Val Tyr Met Leu His Met Met Tyr Gln
                335
                                     340
Ala Met Gly Val Cys Leu Tyr Met Gln Asp Trp Glu Gly Ala Leu
                350
                                     355
Gln Tyr Gly Gln Lys Ile Ile Lys Pro Tyr Ser Lys His Tyr Pro
                365
                                     370
                                                          375
Leu Tyr Ser Leu Asn Val Ala Ser Met Trp Leu Lys Leu Gly Arg
                380
                                     385
                                                          390
Leu Tyr Met Gly Leu Glu His Lys Ala Ala Gly Glu Lys Ala Leu
                395
                                     400
                                                          405
Lys Lys Ala Ile Ala Ile Met Glu Val Ala His Gly Lys Asp His
                410
                                     415
Pro Tyr Ile Ser Glu Ile Lys Gln Glu Ile Glu Ser His
                                     430
```

<210> 40

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<211> 355
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 2112362CD1
<400> 40
Met Ser Val Asn Tyr Ala Ala Gly Leu Ser Pro Tyr Ala Asp Lys
                                       10
Gly Lys Cys Gly Leu Pro Glu Ile Phe Asp Pro Pro Glu Glu Leu
                  20
                                      25
                                                           30
Glu Arg Lys Val Trp Glu Leu Ala Arg Leu Val Trp Gln Ser Ser
                  35
                                       40
                                                           45
Asn Val Val Phe His Thr Gly Ala Gly Ile Ser Thr Ala Ser Gly
                  50
                                      55
Ile Pro Asp Phe Arg Gly Pro His Gly Val Trp Thr Met Glu Glu
                  65
                                      70
Arg Gly Leu Ala Pro Lys Phe Asp Thr Thr Phe Glu Ser Ala Arg
                 80
                                      85
                                                           90
Pro Thr Gln Thr His Met Ala Leu Val Gln Leu Glu Arg Val Gly
                 95
                                     100
                                                          105
Leu Leu Arg Phe Leu Val Ser Gln Asn Val Asp Gly Leu His Val
                 110
                                     115
                                                          120
Arg Ser Gly Phe Pro Arg Asp Lys Leu Ala Glu Leu His Gly Asn
                125
                                     130
Met Phe Val Glu Glu Cys Ala Lys Cys Lys Thr Gln Tyr Val Arg
                140
                                     145
Asp Thr Val Val Gly Thr Met Gly Leu Lys Ala Thr Gly Arg Leu
                155
                                     160
Cys Thr Val Ala Lys Ala Arg Gly Leu Arg Ala Cys Arg Gly Glu
                170
                                     175
                                                          180
Leu Arg Asp Thr Ile Leu Asp Trp Glu Asp Ser Leu Pro Asp Arg
                185
                                     190
Asp Leu Ala Leu Ala Asp Glu Ala Ser Arg Asn Ala Asp Leu Ser
                200
                                     205
                                                          210
Ile Thr Leu Gly Thr Ser Leu Gln Ile Arg Pro Ser Gly Asn Leu
```

```
Pro Leu Ala Thr Lys Arg Arg Gly Gly Arg Leu Val Ile Val Asn
                230
                                     235
Leu Gln Pro Thr Lys His Asp Arg His Ala Asp Leu Arg Ile His
                245
                                     250
                                                          255
Gly Tyr Val Asp Glu Val Met Thr Arg Leu Met Lys His Leu Gly
                260
                                     265
                                                          270
Leu Glu Ile Pro Ala Trp Asp Gly Pro Arg Val Leu Glu Arg Ala
                275
                                     280
                                                          285
Leu Pro Pro Leu Pro Arg Pro Pro Thr Pro Lys Leu Glu Pro Lys
                290
                                     295
                                                          300
Glu Glu Ser Pro Thr Arg Ile Asn Gly Ser Ile Pro Ala Gly Pro
                305
                                     310
                                                          315
Lys Gln Glu Pro Cys Ala Gln His Asn Gly Ser Glu Pro Ala Ser
                320
                                     325
Pro Lys Arg Glu Arg Pro Thr Ser Pro Ala Pro His Arg Pro Pro
                335
                                     340
Lys Arg Val Lys Ala Lys Ala Val Pro Ser
                350
                                     355
```

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<210> 41
<211> 443
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 2117346CD1
<400> 41
Met Asp Arg Leu Gly Ser Phe Ser Asn Asp Pro Ser Asp Lys Pro
  1
                                      10
                                                           15
Pro Cys Arg Gly Cys Ser Ser Tyr Leu Met Glu Pro Tyr Ile Lys
                  20
                                      25
                                                           30
Cys Ala Glu Cys Gly Pro Pro Pro Phe Phe Leu Cys Leu Gln Cys
                  35
                                      40
Phe Thr Arg Gly Phe Glu Tyr Lys Lys His Gln Ser Asp His Thr
                  50
                                      55
                                                           60
Tyr Glu Ile Met Thr Ser Asp Phe Pro Val Leu Asp Pro Ser Trp
                                      70
                  65
                                                           75
Thr Ala Gln Glu Glu Met Ala Leu Leu Glu Ala Val Met Asp Cys
                 80
                                      85
                                                           90
Gly Phe Gly Asn Trp Gln Asp Val Ala Asn Gln Met Cys Thr Lys
                 95
                                     100
Thr Lys Glu Glu Cys Glu Lys His Tyr Met Lys His Phe Ile Asn
                110
                                     115
                                                          120
Asn Pro Leu Phe Ala Ser Thr Leu Leu Asn Leu Lys Gln Ala Glu
                125
                                     130
                                                          135
Glu Ala Lys Thr Ala Asp Thr Ala Ile Pro Phe His Ser Thr Asp
                140
                                     145
Asp Pro Pro Arg Pro Thr Phe Asp Ser Leu Leu Ser Arg Asp Met
                155
                                     160
                                                          165
Ala Gly Tyr Met Pro Ala Arg Ala Asp Phe Ile Glu Glu Phe Asp
                170
                                     175
Asn Tyr Ala Glu Trp Asp Leu Arg Asp Ile Asp Phe Val Glu Asp
                185
                                     190
Asp Ser Asp Ile Leu His Ala Leu Lys Met Ala Val Val Asp Ile
                200
                                     205
                                                         210
```

Tyr His Ser Arg Leu Lys Glu Arg Gln Arg Arg Lys Lys Ile Ile

42/91

```
Arg Asp His Gly Leu Ile Asn Leu Arg Lys Phe Gln Leu Met Glu
                 230
                                      235
                                                          240
Arg Arg Tyr Pro Lys Glu Val Gln Asp Leu Tyr Glu Thr Met Arg
                                      250
                 245
Arg Phe Ala Arg Ile Val Gly Pro Val Glu His Asp Lys Phe Ile
                                      265
                 260
                                                          270
Glu Ser His Ala Leu Glu Phe Glu Leu Arg Arg Glu Ile Lys Arg
                 275
                                      280
                                                          285
Leu Gln Glu Tyr Arg Thr Ala Gly Ile Thr Asn Phe Cys 'Ser Ala
                 290
                                      295
Arg Thr Tyr Asp His Leu Lys Lys Thr Arg Glu Glu Glu Arg Leu
                 305
                                      310
                                                          315
Lys Arg Thr Met Leu Ser Glu Val Leu Gln Tyr Ile Gln Asp Ser
                 320
                                      325
                                                          330
Ser Ala Cys Gln Gln Trp Leu Arg Arg Gln Ala Asp Ile Asp Ser
                335
                                      340
Gly Leu Ser Pro Ser Ile Pro Met Ala Ser Asn Ser Gly Arg Arg
                350
                                      355
                                                          360
Ser Ala Pro Pro Leu Asn Leu Thr Gly Leu Pro Gly Thr Glu Lys
                365
                                     370
                                                          375
Leu Asn Glu Lys Glu Lys Glu Leu Cys Gln Met Val Arg Leu Val
                380
                                     385
                                                          390
Pro Gly Ala Tyr Leu Glu Tyr Lys Ser Ala Leu Leu Asn Glu Cys
                395
                                      400
                                                          405
Asn Lys Gln Gly Gly Leu Arg Leu Ala Gln Ala Arg Ala Leu Ile
                410
                                      415
Lys Ile Asp Val Asn Lys Thr Arg Lys Ile Tyr Asp Phe Leu Ile
                425
                                     430
                                                          435
Arg Glu Gly Tyr Ile Thr Lys Gly
                440
```

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<210> 42
<211> 164
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 2119917CD1
<400> 42
Met Thr Ala Ser Ala Gln Pro Arg Gly Arg Arg Pro Gly Val Gly
                  5
                                      10
                                                           15
Val Gly Val Val Thr Ser Cys Lys His Pro Arg Cys Val Leu
                 20
                                      25
Leu Gly Lys Arg Lys Gly Ser Val Gly Ala Gly Ser Phe Gln Leu
                 35
                                      40
Pro Gly Gly His Leu Glu Phe Gly Glu Thr Trp Glu Glu Cys Ala
                 50
                                      55
                                                           60
Gln Arg Glu Thr Trp Glu Glu Ala Ala Leu His Leu Lys Asn Val
                 65
                                      70
                                                          75
His Phe Ala Ser Val Val Asn Ser Phe Ile Glu Lys Glu Asn Tyr
                 80
                                                          90
                                      85
His Tyr Val Thr Ile Leu Met Lys Gly Glu Val Asp Val Thr His
                 95
                                     100
                                                         105
Asp Ser Glu Pro Lys Asn Val Glu Pro Glu Lys Asn Glu Ser Trp
                110
                                     115
                                                         120
Glu Trp Val Pro Trp Glu Glu Leu Pro Pro Leu Asp Gln Leu Phe
                125
                                     130
```

43/91

145

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<210> 43
<211> 215
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 2123456CD1
Met Leu Gly Ala Glu Trp Ser Lys Leu Gln Pro Thr Glu Lys Gln
                                     10
 1
Arg Tyr Leu Asp Glu Ala Glu Arg Glu Lys Gln Gln Tyr Met Lys
                                     25
                 20
Glu Leu Arg Ala Tyr Gln Gln Ser Glu Ala Tyr Lys Met Cys Thr
                                     40
                                                           45
                 35
Glu Lys Ile Gln Glu Lys Lys Ile Lys Lys Glu Asp Ser Ser Ser
                                                           60
                 50
                                     55
Gly Leu Met Asn Thr Leu Leu Asn Gly His Lys Gly Gly Asp Cys
                                     70
                                                           75
                 65
Asp Gly Phe Ser Thr Phe Asp Val Pro Ile Phe Thr Glu Glu Phe
                                                           90
                 80
                                     85
Leu Asp Gln Asn Lys Ala Arg Glu Ala Glu Leu Arg Arg Leu Arg
                                    100
                                                          105
                 95
Lys Met Asn Val Ala Phe Glu Glu Gln Asn Ala Val Leu Gln Arg
                110
                                    115
                                                          120
His Thr Gln Ser Met Ser Ser Ala Arg Glu Arg Leu Glu Gln Glu
                                    130
                                                          135
                125
Leu Ala Leu Glu Glu Arg Arg Thr Leu Ala Leu Gln Gln Leu
                140
                                    145
Gln Ala Val Arg Gln Ala Leu Thr Ala Ser Phe Ala Ser Leu Pro
                                    160
                155
Val Pro Gly Thr Gly Glu Thr Pro Thr Leu Gly Thr Leu Asp Phe
                                                         180
                170
                                    175
Tyr Met Ala Arg Leu His Gly Ala Ile Glu Arg Asp Pro Ala Gln
                                    190
                                                         195
                185
His Glu Lys Leu Ile Val Arg Ile Lys Glu Ile Leu Ala Gln Val
                                    205
                200
Ala Ser Glu His Leu
                215
```

Trp Gly Leu Arg Cys Leu Lys Glu Gln Gly Tyr Asp Pro Phe Lys

Glu Asp Leu Asn His Leu Val Gly Tyr Lys Gly Asn His Leu

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<210> 44

<211> 539

<212> PRT

<213> Homo sapiens

<220>

<221> misc-feature

<223> Incyte ID No.: 2148792CD1

<400> 44
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WO 00/44900

PCT/US00/02237

Met 1	Ala	Ala	Leu	Phe 5	Leu	Ser	Ala	Pro	Pro 10	Gln	Ala	Glu	Val	Thr 15
Phe	Glu	Asp	Val	Ala 20	Val	Tyr	Leu	Ser	Arg 25	Glu	Glu	Trp	Gly	Arg 30
Leu	Gly	Pro	Ala	Gln 35	Arg	Gly	Leu	Tyr	Arg 40	Asp	Val	Met	Leu	Glu 45
Thr	Tyr	Gly	Asn	Leu 50	Val	Ser	Leu	Gly	Val 55	Gly	Pro	Ala	Gly	Pro 60
Lys	Pro	Gly	Val	Ile 65	Ser	Gln	Leu	Glu	Arg 70	Gly	Asp	Glu	Pro	<b>T</b> rp 75
				80					Lуs 85					90
				95					Glu 100					105
Ser	Gln	Glu	Thr	Phe 110	Gly	Glu	Glu		Pro 115					120
				125				_	130					135
_				140					Ala 145					150
_				155					Asn 160					165
				170					Lys 175					180
				185					Asn 190					195
				200					Arg 205					210
				215					Asp 220					225
				230					Cys 235					240
_				245					Arg 250					255
				260					Lys 265					270
				275					His 280					285
				290					Phe 295					300
				305					Gly 310					315
_				320					Ala 325					330
_				335					Lys 340					345
				350					Ser 355					360
				365					Phe 370					375
				380					Leu 385					390
				395					Cys 400					405
				410					Glu 415					420
				425					Asp 430					435
				440					Gln 445					450
Glu	Lys	Pro	Tyr	Lys 455	Cys	Ser	Glu	Cys	Gly 460	Lys	Ala	Phe	His	Asn 465

45/91

```
Ser Ser Arg Leu Ile His His Gln Arg Leu His His Gly Glu Lys
                                                          480
                                     475
                470
Pro Tyr Arg Cys Ser Asp Cys Lys Lys Ala Phe Ser Gln Ser Thr
                                     490
                                                          495
                485
Tyr Leu Ile Gln His Arg Arg Ile Hıs Thr Gly Glu Lys Pro Tyr
                                                         510
                                     505
                500
Lys Cys Ser Glu Cys Gly Lys Ala Phe Arg His Ser Ser Asn Met
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                                                          525
                515
Cys Gln His Gln Arg Ile His Leu Arg Glu Asp Phe Ser Met
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                530
```

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<212> PRT
<213> Homo sapiens
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<221> misc-feature
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Ala Pro Arg Arg Ala Val Arg Gly Gln Ala Gly Gly Gly Pro
                                      25
                                                           30
                  20
Gly Thr Gly Pro Gly Leu Gly Glu Ala Gly Ser Leu Ala Thr Cys
                                                           45
                                      40
                  35
Glu Leu Pro Leu Ala Lys Ser Glu Trp Gln Lys Lys Leu Thr Pro
                                      55
                                                           60
                  50
Glu Gln Phe Tyr Val Thr Arg Glu Lys Gly Thr Glu Pro Pro Phe
                                                           75
                  65
                                      70
Ser Gly Ile Tyr Leu Asn Asn Lys Glu Ala Gly Met Tyr His Cys
                                                           90
                  80
                                      85
Val Cys Cys Asp Ser Pro Leu Phe Ser Ser Glu Lys Lys Tyr Cys
                                     100
                                                          105
                  95
Ser Gly Thr Gly Trp Pro Ser Phe Ser Glu Ala His Gly Thr Ser
                                                          120
                                     115
                 110
Gly Ser Asp Glu Ser His Thr Gly Ile Leu Arg Arg Leu Asp Thr
                                                          135
                 125
                                     130
Ser Leu Gly Ser Ala Arg Thr Glu Val Val Cys Lys Gln Cys Glu
                                     145
                                                          150
                 140
Ala His Leu Gly His Val Phe Pro Asp Gly Pro Gly Pro Asn Gly
                                     160
                 155
Gln Arg Phe Cys Ile Asn Ser Val Ala Leu Lys Phe Lys Pro Arg
                 170
Lys His
```

```
<210> 46
<211> 534
<212> PRT
<213> Homo sapiens
<220>
<221> misc-feature
<223> Incyte ID No.: 3128913CD1
```

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# PCT/US00/02237

# WO 00/44900

-400	)> 46	5												
Met 1	Ala	Val	Glu	Ser 5	Gly	Val	Ile	Ser	Thr 10	Leu	Ile	Pro	Gln	Asp 15
	Pro	Glu	Gln	Glu 20	Leu	Ile	Leu	Val	Lys 25	Val	Glu	Asp	Asn	Phe 30
ser	Trp	Asp	Glu	Lys 35	Phe	Lys	Gln	Asn	Gly 40	Ser	Thr	Gln	Ser	Cys 45
Gln	Glu	Leu	Phe	Arg 50	Gln	Gln	Phe	Arg	Lys 55	Phe	Cys	Tyr	Gln	Glu 60
Thr	Pro	Gly	Pro	Arg 65	Glu	Ala	Leu	Ser	Arg 70	Leu	Gln	Glu	Leu	Cys 75
Tyr	Gln	Trp	Leu	Met 80	Pro	Glu	Leu	His	85		Glu			90
				95		Gln			100		Leu			105
				110					115		Ser			120
				125					130		Phe			135
_				140					145		Ala			150
_				155					160		Ser			165
				170					175		Trp			180
				185					190		Thr			195
				200					205		Pro			210
				215					220		Leu			225
				230					235		Pro			240
				245					250		Ser			255 Thr
				260					265		Ile Glu			270
				275					280		His			285
				290					295		Pro			300
				305					310		Tyr			315
				320					325		Glu			330
				335					340		Ile			345
				350					355		Asn			360
				365					370		His			375
				380					385		Cys			390
				395					400		Arg			405
				410					415		Lys			420
				425					430		His			435
				440					445		Phe			450
دور	-10	~ y ~		-75	~		-1-	1						

465

WO 00/44900 PCT/US00/02237

460

475

490

Ser Asn Leu Ile Arg His Gln Arg Ile His Ser Gly Glu Glu Pro

Tyr Gln Cys Asn Glu Cys Gly Lys Thr Phe Lys Arg Ser Ser Ala

455

470

```
Leu Val Gln His Gln Arg Ile His Ser Gly Asp Glu Ala Tyr Ile
                                     505
                                                          510
                500
Cys Asn Glu Cys Gly Lys Ala Phe Arg His Arg Ser Val Leu Met
                515
Arg His Gln Arg Val His Thr Ile Lys
                530
<210> 47
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Met Ser Thr Gly Ser Val Ser Asp Pro Glu Glu Met Glu Leu Arg
                                      10
                  5
 1
Gly Leu Gln Arg Glu Tyr Pro Val Pro Ala Ser Lys Arg Pro Pro
                                      25
                 20
Leu Arg Gly Val Glu Arg Ser Tyr Ala Ser Pro Ser Asp Asn Ser
                 35
                                      40
                                                           45
Ser Ala Glu Glu Glu Asp Pro Asp Gly Glu Glu Arg Cys Ala
                                      55
                                                           60
                 50
                                         Lys Arg Lys Arg Pro
Leu Gly Thr Ala Gly Ser Ala Glu Gly Cys
                                      70
                 65
Arg Val Ala Gly Gly Gly Ala Gly Gly Ser Ala Gly Gly Gly
                                                           90
                                      85
                 80
Gly Lys Lys Pro Leu Pro Ala Lys Gly Ser Ala Ala Glu Cys Lys
                                                         105
                 95
                                     100
Gln Ser Gln Arg Asn Ala Ala Asn Ala Arg Glu Arg Ala Arg Met
                                     115
                                                          120
                110
Arg Val Leu Ser Lys Ala Phe Ser Arg Leu Lys Thr Ser Leu Pro
                                                          135
                                     130
                125
Trp Val Pro Pro Asp Thr Lys Leu Ser Lys Leu Asp Thr Leu Arg
                                                         150
                140
                                     145
Leu Ala Ser Ser Tyr Ile Ala His Leu Arg Gln Leu Leu Gln Glu
                155
                                     160
Asp Arg Tyr Glu Asn Gly Tyr Val His Pro Val Asn Leu Thr Trp
                                     175
                170
Pro Phe Val Val Ser Gly Arg Pro Asp Ser Asp Thr Lys Glu Val
                                     190
                                                         195
                185
Ser Ala Ala Asn Arg Leu Cys Gly Thr Thr Ala
                200
                                     205
<210> 48
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<212> PRT
<213> Homo sapiens
```

48/91

```
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<223> Incyte ID No.: 3286656CD1
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                                      10
Glu Trp Ala Leu Leu Asp Ser Ala Arg Arg Ser Leu Cys Lys Tyr
                 20
                                      25
Arg Met Leu Asp Gln Cys Arg Thr Leu Ala Ser Arg Gly Thr Pro
                 35
                                      40
Pro Cys Lys Pro Ser Cys Val Ser Gln Leu Gly Gln Arg Ala Glu
                 50
                                      55
                                                           60
Pro Lys Ala Thr Glu Arg Gly Ile Leu Arg Ala Thr Gly Val Ala
                 65
                                      70
Trp Glu Ser Gln Leu Lys Pro Glu Glu Leu Pro Ser Met Gln Asp
                 80
                                      85
Leu Leu Glu Glu Ala Ser Ser Arg Asp Met Gln Met Gly Pro Gly
                 95
                                     100
                                                          105
Leu Phe Leu Arg Met Gln Leu Val Pro Ser Ile Glu Glu Arg Glu
                110
                                     115
                                                          120
Thr Pro Leu Thr Arg Glu Asp Arg Pro Ala Leu Gln Glu Pro Pro
                125
                                     130
                                                          135
Trp Ser Leu Gly Cys Thr Gly Leu Lys Ala Ala Met Gln Ile Gln
                140
                                     145
Arg Val Val Ile Pro Val Pro Thr Leu Gly His Arg Asn Pro Trp
                155
                                     160
                                                          165
Val Ala Arg Asp Ser Ala Met
                170
```

<220>

<210> 49

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<212> PRT
<213> Homo sapiens
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Met Gly Pro Leu Gln Phe Arg Asp Val Ala Ile Glu Phe Ser Leu
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                                     10
Glu Glu Trp His Cys Leu Asp Thr Ala Gln Arg Asn Leu Tyr Arg
                                      25
                 20
Asp Val Met Leu Glu Asn Tyr Arg Asn Leu Val Phe Leu Gly Ile
                                     40
                 35
Val Val Ser Lys Pro Asp Leu Val Thr Cys Leu Glu Gln Gly Lys
                 50
                                     55
Lys Pro Leu Thr Met Glu Arg His Glu Met Ile Ala Lys Pro Pro
                 65
                                     70
                                                          75
Val Met Ser Ser His Phe Ala Gln Asp Leu Trp Pro Glu Asn Ile
                 80
                                     85
Gln Asn Ser Phe Gln Ile Gly Met Leu Arg Arg Tyr Glu Glu Cys
                                                         105
                 95
                                    100
Arg His Asp Asn Leu Gln Leu Lys Lys Gly Cys Lys Ser Val Gly
                                    115
                110
Glu His Lys Val His Lys Gly Gly Tyr Asn Gly Leu Asn Gln Cys
                125
                                    130
Leu Thr Thr Gln Lys Glu Ile Phe Gln Cys Asp Lys Tyr Gly
```

## PCT/US00/02237

```
145
                 140
Lys Val Phe His Lys Phe Ser Asn Ser Asn Thr Tyr Lys Thr Arg
                                     160
                155
His Thr Gly Ile Asn Leu Phe Lys Cys Ile Ile Cys Gly Lys Ala
                                     175
                 170
Phe Lys Arg Ser Ser Thr Leu Thr Thr His Lys Lys Ile His Thr
                                                          195
                                     190
                 185
Gly Glu Lys Pro Tyr Lys Cys Glu Glu Cys Gly Lys Ala Phe Asn
                                     205
                                                          210
                 200
Gin Ser Ser Asn Leu Thr Thr His Lys Arg Ile His Thr Gly Glu
                                     220
                 215
Lys Pro Tyr Lys Cys Glu Glu Cys Gly Lys Ala Phe Asn Trp Ser
                                                          240
                                     235
                 230
Ser Asp Leu Asn Lys His Lys Lys Ile His Ile Glu Arg Lys Pro
                                     250
                 245
```

Tyr Ile Val Lys Asn Val Thr Asp Leu Leu Asn Val Pro Pro Leu

WO 00/44900

Leu Ile Ser Ile Arg

```
<210> 50
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<212> PRT
<213> Homo sapiens
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<221> misc-feature
<223> Incyte ID No.: 3507366CD1
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Met Asp Lys Arg Tyr Leu Gln Phe Asp Ile Lys Ala Phe Val Glu
                                      10
                   5
Asn Asn Pro Ala Ile Lys Trp Cys Pro Thr Pro Gly Cys Asp Arg
                  20
                                      25
Ala Val Arg Leu Thr Lys Gln Gly Ser Asn Thr Ser Gly Ser Asp
                                                           45
                                       40
                  35
Thr Leu Ser Phe Pro Leu Leu Arg Ala Pro Ala Val Asp Cys Gly
                                                           60
                                      55
                  50
Lys Gly His Leu Phe Cys Trp Glu Cys Leu Gly Glu Ala His Glu
                                                           75
                                      70
                  65
Pro Cys Asp Cys Gln Thr Trp Lys Asn Trp Leu Gln Lys Ile Thr
                                                           90
                                      85
                  80
Glu Met Lys Pro Glu Glu Leu Val Gly Val Ser Glu Ala Tyr Glu
                                     100
                  95
Asp Ala Ala Asn Cys Leu Trp Leu Leu Thr Asn Ser Lys Pro Cys
                                                          120
                                     115
                 110
Ala Asn Cys Lys Ser Pro Ile Gln Lys Asn Glu Gly Cys Asn His
                                                          135
                                     130
                 125
Met Gln Cys Ala Lys Cys Lys Tyr Asp Phe Cys Trp Ile Cys Leu
                                                          150
                                     145
                 140
Glu Glu Trp Lys Lys His Ser Ser Ser Thr Gly Gly Tyr Tyr Arg
                                                          165
                                     160
                 155
Cys Thr Arg Tyr Glu Val Ile Gln His Val Glu Glu Gln Ser Lys
                 170
                                     175
Glu Met Thr Val Glu Ala Glu Lys Lys His Lys Arg Phe Gln Glu
                                     190
                 185
Leu Asp Arg Phe Met His Tyr Tyr Thr Arg Phe Lys Asn His Glu
                                     205
                 200
His Ser Tyr Gln Leu Glu Gln Arg Leu Leu Lys Thr Ala Lys Glu
```

50/91

### SUBSTITUTE SHEET (RULE 26)

225

WO 00/44900 PCT/US00/02237

220

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Lys Met Glu Gln Met Ser Arg Val Ser Lys Asn
                230
                                     235
<210> 51
<211> 214
<212> PRT
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Met Asn Leu Ser Ser Ala Ser Ser Thr Glu Glu Lys Ala Val Thr
  1
                  5
                                      10
Thr Val Leu Trp Gly Cys Glu Leu Ser Gln Glu Arg Arg Thr Trp
                 20
                                                           30
Thr Phe Arg Pro Gln Leu Glu Gly Lys Gln Ser Cys Arg Leu Leu
                                      40
                 35
Leu His Thr Ile Cys Leu Gly Glu Lys Ala Lys Glu Glu Met His
                                      55
                                                           60
                 50
Arg Val Glu Ile Leu Pro Pro Ala Asn Gln Glu Asp Lys Lys Met
                 65
                                      70
Gln Pro Val Thr Ile Ala Ser Leu Gln Ala Ser Val Leu Pro Met
                                     85
                 80
Val Ser Met Val Gly Val Gln Leu Ser Pro Pro Val Thr Phe Gln
                 95
                                    100
                                                         105
Leu Arg Ala Gly Ser Gly Pro Val Phe Leu Ser Gly Gln Glu Arg
                                                         120
                110
                                    115
Tyr Glu Ala Ser Asp Leu Thr Trp Glu Glu Glu Glu Glu Glu Glu
                                                         135
                125
                                    130
Gly Glu Glu Glu Glu Glu Glu Glu Asp Asp Glu Asp Glu Asp
                                                         150
                                    145
                140
Ala Asp Ile Ser Leu Glu Glu Gln Ser Pro Val Lys Gln Val Lys
                155
                                    160
                                                         165
Arg Leu Val Pro Gln Lys Gln Ala Ser Val Ala Lys Lys Lys
                                    175
                                                         180
                170
Leu Glu Lys Glu Glu Glu Ile Arg Ala Ser Val Arg Asp Lys
                                    190
                                                         195
                185
Ser Pro Val Lys Lys Ala Lys Ala Thr Ala Arg Ala Lys Lys Pro
                200
                                    205
                                                         210
Gly Phe Lys Lys
<210> 52
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<212> PRT
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<221> misc-feature
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Met Asn Phe Thr Val Gly Phe Lys Pro Leu Leu Gly Asp Ala His
```

215

51/91

```
1
Ser Met Asp Asn Leu Glu Lys Gln Leu Ile Cys Pro Ile Cys Leu
                 20
                                      25
Glu Met Phe Ser Lys Pro Val Val Ile Leu Pro Cys Gln His Asn
                 35
                                      40
Leu Cys Arg Lys Cys Ala Asn Asp Val Phe Gln Ala Ser Asn Pro
                 50
                                      55
Leu Trp Gln Ser Arg Gly Ser Thr Thr Val Ser Ser Gly Gly Arg
                                      70
                 65
Phe Arg Cys Pro Ser Cys Arg His Glu Val
                                         Val Leu Asp Arg His
                 80
                                      85
                                                           90
Gly Val Tyr Gly Leu Gln Arg Asn Val Leu Val Glu Asn Ile Ile
                                     100
Asp Ile Tyr Lys Gln Glu Ser Ser Lys Pro Leu His Ser Lys Ala
                110
                                     115
Glu Gln His Leu Met Cys Glu Glu His Glu Glu Glu Lys Ile Asn
                125
                                     130
                                                          135
Ile Tyr Cys Leu Ser Cys Glu Val Pro Thr Cys Ser Leu Cys Lys
                140
                                     145
                                                          150
Val Phe Gly Ala His Lys Asp Cys Glu Val Ala Pro Leu Pro Thr
                155
                                     160
Ile Tyr Lys Arg Gln Lys Ser Glu Leu Ser Asp Gly Ile Ala Met
                                     175
                170
Leu Val Ala Gly Asn Asp Arg Val Gln Ala Val Ile Thr Gln Met
                185
                                     190
Glu Glu Val Cys Gln Thr Ile Glu Asp Asn Ser Arg Arg Gln Lys
                200
                                     205
                                                          210
Gln Leu Leu Asn Gln Arg Phe Glu Ser Leu Cys Ala Val Leu Glu
                                     220
                215
Glu Arg Lys Gly Glu Leu Leu Gln Ala Leu Ala Arg Glu Gln Glu
                230
                                     235
Glu Lys Leu Gln Arg Val Arg Gly Leu Ile Arg Gln Tyr Gly Asp
                245
                                     250
                                                          255
His Leu Glu Ala Ser Ser Lys Leu Val Glu Ser Ala Ile Gln Ser
                                     265
                260
Met Glu Glu Pro Gln Met Ala Leu Tyr Leu Gln Gln Ala Lys Glu
                                     280
                275
                                                         285
Leu Ile Asn Lys Val Gly Ala Met Ser Lys Val Glu Leu Ala Gly
                290
                                     295
                                                          300
Arg Pro Glu Pro Gly Tyr Glu Ser Met Glu Gln Phe Thr Val Arg
                305
                                     310
Val Glu His Val Ala Glu Met Leu Arg Thr Ile Asp Phe Gln Pro
                                     325
                                                         330
                320
Gly Ala Ser Gly Gly Gly Arg Gly Gly Pro Arg Arg Lys Lys
                335
                                     340
Arg Ala Thr Arg Gly Pro Glu Glu Lys Thr Ala Arg Met Gly Pro
                350
                                     355
Tyr Arg Pro Leu Arg Pro Asn Pro Asp Pro Leu Leu Arg Lys Ser
                365
                                     370
                                                         375
Pro Arg Arg Leu Arg Ile Ser Gly Gly Arg Asn Ser Cys Arg Lys
                                                         390
                                    385
                380
Lys Thr Pro Ala Ser Phe
                395
```

<sup>&</sup>lt;210> 53

<sup>&</sup>lt;211> 486

<sup>&</sup>lt;212> PRT <213> Homo sapiens

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<220>
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<223> Incyte ID No.: 3633422CD1
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Met Arg Arg Leu Val His Asp Leu Leu Pro Pro Glu Val Cys Ser
                                      10
Leu Leu Asn Pro Ala Ala Ile Tyr Ala Asn Asn Glu Ile Ser Leu
                 20
                                      25
                                         Asp Tyr Thr Leu Ala
Arg Asp Val Glu Val Tyr Gly Phe Asp Tyr
                 35
                                      40
                                                           45
Gln Tyr Ala Asp Ala Leu His Pro Glu Ile Phe Ser Thr Ala Arg
                                      55
                                                           60
                 50
Asp Ile Leu Ile Glu His Tyr Lys Tyr Pro Glu Gly Ile Arg Lys
                                      70
                 65
Tyr Asp Tyr Asn Pro Ser Phe Ala Ile Arg Gly Leu His Tyr Asp
                                                           90
                                      85
                 80
Ile Gln Lys Ser Leu Leu Met Lys Ile Asp Ala Phe His Tyr Val
                                     100
                                                          105
                 95
Gln Leu Gly Thr Ala Tyr Arg Gly Leu Gln Pro Val Pro Asp Glu
                                     115
                                                          120
                110
Glu Val Ile Glu Leu Tyr Gly Gly Thr Gln His Ile Pro Leu Tyr
                                                          135
                125
                                     130
Gln Met Ser Gly Phe Tyr Gly Lys Gly Pro Ser Ile Lys Gln Phe
                140
                                     145
Met Asp Ile Phe Ser Leu Pro Glu Met Ala Leu Leu Ser Cys Val
                                     160
                                                          165
                155
Val Asp Tyr Phe Leu Gly His Ser Leu Glu Phe Asp Gln Ala His
                                                          180
                                     175
                170
Leu Tyr Lys Asp Val Thr Asp Ala Ile Arg Asp Val His Val Lys
                                     190
                185
Gly Leu Met Tyr Gln Trp Ile Glu Gln Asp Met Glu Lys Tyr Ile
                                                          210
                200
                                     205
Leu Arg Gly Asp Glu Thr Phe Ala Val Leu Ser Arg Leu Val Ala
                                     220
                215
His Gly Lys Gln Leu Phe Leu Ile Thr Asn Ser Pro Phe Ser Phe
                                     235
                230
Val Asp Lys Gly Met Arg His Met Val Gly Pro Asp Trp Arg Gln
                                     250
                245
Leu Phe Asp Val Val Ile Val Gln Ala Asp Lys Pro Ser Phe Phe
                                                          270
                260
                                     265
Thr Asp Arg Arg Lys Pro Phe Arg Lys Leu Asp Glu Lys Gly Ser
                275
                                     280
                                                          285
Leu Gln Trp Asp Arg Ile Thr Arg Leu Glu Lys Gly Lys Ile Tyr
                                                          300
                                     295
                290
Arg Gln Gly Asn Leu Phe Asp Phe Leu Arg Leu Thr Glu Trp Arg
                 305
                                     310
Gly Pro Arg Val Leu Tyr Phe Gly Asp His Leu Tyr Ser Asp Leu
                                     325
                                                          330
                320
Ala Asp Leu Met Leu Arg His Gly Trp Arg Thr Gly Ala Ile Ile
                                                          345
                335
                                     340
Pro Glu Leu Glu Arg Glu Ile Arg Ile Ile Asn Thr Glu Gln Tyr
                                     355
                 350
Met His Ser Leu Thr Trp Gln Gln Ala Leu Thr Gly Leu Leu Glu
                                                          375
                                     370
                 365
Arg Met Gln Thr Tyr Gln Asp Ala Glu Ser Arg Gln Val Leu Ala
                                     385
                380
Ala Trp Met Lys Glu Arg Gln Glu Leu Arg Cys Ile Thr Lys Ala
                 395
                                     400
Leu Phe Asn Ala Gln Phe Gly Ser Ile Phe Arg Thr Phe His Asn
                                     415
                                                          420
                 410
Pro Thr Tyr Phe Ser Arg Arg Leu Val Arg Phe Ser Asp Leu Tyr
```

53/91

2.1.1994 · 展 酸15

WO 00/44900 PCT/US00/02237

```
Met Ala Ser Leu Ser Cys Leu Leu Asn Tyr Arg Val Asp Phe Thr
                 440
                                      445
Phe Tyr Pro Arg Arg Thr Pro Leu Gln His Glu Ala Pro Leu Trp
                 455
                                      460
                                                          465
Met Asp Gln Leu Cys Thr Gly Cys Met Lys Thr Pro Phe Leu Gly
                470
                                      475
                                                          480
Asp Met Ala His Ile Arg
                485
<210> 54
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<212> PRT
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                                                         Ser
Ala Ala Leu Asp Cys
                                                           30
                 20
                                       25
                    Ser Gln Thr Ser Thr
                                         Ser Ile Phe Ala Ser
Leu Leu Ala Asp Asp
                                                           45
                 35
                                       40
Pro Thr Ser Pro Pro Val Leu Gly Glu Ser Val Leu Gln Asp Asn
                                       55
                                                           60
                 50
Ser Phe Asp Leu Asn Asn Gly Ser Asp Ala Glu Glu Glu Met
                                      70
                 65
Glu Thr Gln Ser Ser Asp Phe Pro Pro Ser Leu Thr Gln Pro Ala
                                                           90
                                      85
                 80
Pro Asp Gln Ser Ser Thr Ile Gln Leu His Pro Ala Thr Ser Pro
                                                          105
                 95
                                      100
Ala Val Ser Pro Thr Thr Ser Pro Ala Val Ser Leu Val Val Ser
                                     115
                                                          120
                110
Pro Ala Ala Ser Pro Glu Ile Ser Pro Glu Val Cys Pro Ala Ala
                125
                                     130
Ser Thr Val Val Ser Pro Ala Val Phe Ser Val Val Ser Pro Ala
                                                          150
                                     145
                140
Ser Ser Ala Val Leu Pro Ala Val Ser Leu Glu Val Pro Leu Thr
                155
                                     160
                                                          165
Ala Ser Val Thr Ser Pro Lys Ala Ser Pro Val Thr Ser Pro Ala
                170
                                     175
Ala Ala Phe Pro Thr Ala Ser Pro Ala Asn Lys Asp Val Ser Ser
                                     190
                185
Phe Leu Glu Thr Thr Ala Asp Val Glu Glu Ile Thr Gly Glu Gly
                200
                                     205
                                                          210
Leu Thr Ala Ser Gly Ser Gly Asp Val Met Arg Arg Arg Ile Ala
                                     220
                215
Thr Pro Glu Glu Val Arg Leu Pro Leu Gln His Gly Trp Arg Arg
                                                          240
                230
                                     235
Glu Val Arg Ile Lys Asn Ser Ser His Arg Trp Gln Gly Glu Thr
                245
                                     250
                                                          255
Trp Tyr Tyr Gly Pro Cys Gly Lys Arg Met Lys Gln Phe Pro Glu
                                                          270
                                     265
                260
Val Ile Lys Tyr Leu Ser Arg Asn Val Val His Ser Val Arg Arg
                                     280
                275
```

Glu His Phe Ser Phe Ser Pro Arg Met Pro Val Gly Asp Phe Phe

54/91

```
300
                290
                                    295
Glu Glu Arg Asp Thr Pro Glu Gly Leu Gln Trp Val Gln Leu Ser
                305
                                    310
Ala Glu Glu Ile Pro Ser Arg Ile Gln Ala Ile Thr Gly Lys Arg
                                                          330
                320
                                    325
Gly Arg Pro Arg Asn Thr Glu Lys Ala Lys Thr Lys Glu Val Pro
                335
                                    340
                                                         345
Lys Val Lys Arg Gly Arg Gly Arg Pro Pro Lys Val Lys Ile Thr
                350
                                    355
                                                         360
Glu Leu Leu Asn Lys Thr Asp Asn Arg Pro Leu Lys Lys Leu Glu
                365
                                    370
Ala Gln Glu Thr Leu Asn Glu Glu Asp Lys Ala Lys Ile Ala Lys
                                                         390
                380
                                    385
Ser Lys Lys Met Arg Gln Lys Val Gln Arg Gly Glu Cys Gln
                395
                                    400
Thr Thr Ile Gln Gly Gln Ala Arg Asn Lys Arg Lys Gln Glu Thr
                410
                                    415
                                                         420
Lys Ser Leu Lys Gln Lys Glu Ala Lys Lys Lys Ser Lys Ala Glu
                                    430
                                                          435
                425
Lys Glu Lys Gly Lys Thr Lys Gln Glu Lys Leu Lys Glu Lys Val
                440
                                    445
                                                         450
Lys Arg Glu Lys Lys Glu Lys Val Lys Met Lys Glu Lys Glu Glu
                                    460
                455
Val Thr Lys Ala Lys Pro Ala Cys Lys Ala Asp Lys Thr Leu Ala
                                    475
                470
Thr Gln Arg Arg Leu Glu Glu Arg Gln Arg Gln Gln Met Ile Leu
                                                         495
                485
                                    490
Glu Asp Met Lys Lys Pro Thr Glu Asp Met Cys Leu Thr Asp His
                500
                                    505
                                                         510
Gln Pro Leu Pro Asp Phe Ser Arg Val Pro Gly Leu Thr Leu Pro
                                    520
                                                         525
                515
Ser Gly Ala Phe Ser Asp Cys Leu Thr Ile Val Glu Phe Leu His
                                    535
                530
Ser Phe Gly Lys Val Leu Gly Leu Asp Pro Ala Gln Gly Cys Ala
                                    550
```

Asp

55/91

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## SUBSTITUTE SHEET (RULE 26)

#### PCT/US00/02237

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WO 00/44900

生物。 推進以於國際企業所述的經歷數數的例如多於學科生發展的論言可以的語言

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58/91

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69/91

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70/91

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75/91

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76/91

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77/91

**建筑设施设施设施** 

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78/91

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79/91

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80/91

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86/91

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## PCT/US00/02237

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90/91

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aaqaatgqac tgccccnta agaaacctgt ttgagaatca ctgaattata aatataaacc 780
cagat
```

最后,我们,但还是我们要要还要得到这些人事情况,在我们就是是我们的自己的人就不是